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- (71) Applicant: MANKIND CORPORATION [US/US];
28903 North Avenue Paine, Valencia, CA 91355 (US).
- (72) Inventors: SIMARD, John, J., L.; Suite #7, 1684 Alberni
Street, Vancouver, British Columbia V6G1A6 (CA). DIA-
MOND, David, C.; 23135 Schoenborn Street, West Hills,
CA 91304 (US). LIU, Liping; 22228 Victory Boulevard,
H-111, Woodland Hills, CA 91367 (US). LIU, Zheng;
22216 Victory Boulevard, C302, Woodland Hills, CA
91367 (US).
- (74) Agent: MALLON, Joseph, J.; KNOBBE, MARTENS,
OLSON & BEAR, LLP, 2040 Main Street, 14th Floor,
Irvine, CA 92614 (US).
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(54) Title: EPITOPE SEQUENCES

(57) Abstract: Disclosed herein are polypeptides, including epitopes, clusters, and antigens. Also disclosed are compositions that include said polypeptides and methods for their use.

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EPITOPE SEQUENCES

Background of the Invention

Field of the Invention

5 The present invention generally relates to peptides, and nucleic acids encoding peptides, that are useful epitopes of target-associated antigens. More specifically, the invention relates to epitopes that have a high affinity for MHC class I and that are produced by target-specific proteasomes.

Description of the Related Art

10 Neoplasia and the Immune System

 The neoplastic disease state commonly known as cancer is thought to result generally from a single cell growing out of control. The uncontrolled growth state typically results from a multi-step process in which a series of cellular systems fail, resulting in the genesis of a neoplastic cell. The resulting neoplastic cell rapidly reproduces itself, forms one or more tumors, and eventually
15 may cause the death of the host.

 Because the progenitor of the neoplastic cell shares the host's genetic material, neoplastic cells are largely unassailed by the host's immune system. During immune surveillance, the process in which the host's immune system surveys and localizes foreign materials, a neoplastic cell will appear to the host's immune surveillance machinery as a "self" cell.

20 Viruses and the Immune System

 In contrast to cancer cells, virus infection involves the expression of clearly non-self antigens. As a result, many virus infections are successfully dealt with by the immune system with minimal clinical sequela. Moreover, it has been possible to develop effective vaccines for many of those infections that do cause serious disease. A variety of vaccine approaches have been used
25 successfully to combat various diseases. These approaches include subunit vaccines consisting of individual proteins produced through recombinant DNA technology. Notwithstanding these advances, the selection and effective administration of minimal epitopes for use as viral vaccines has remained problematic.

 In addition to the difficulties involved in epitope selection stands the problem of viruses
30 that have evolved the capability of evading a host's immune system. Many viruses, especially viruses that establish persistent infections, such as members of the herpes and pox virus families, produce immunomodulatory molecules that permit the virus to evade the host's immune system. The effects of these immunomodulatory molecules on antigen presentation may be overcome by the targeting of select epitopes for administration as immunogenic compositions. To better
35 understand the interaction of neoplastic cells and virally infected cells with the host's immune system, a discussion of the system's components follows below.

The immune system functions to discriminate molecules endogenous to an organism ("self" molecules) from material exogenous or foreign to the organism ("non-self" molecules). The immune system has two types of adaptive responses to foreign bodies based on the components that mediate the response: a humoral response and a cell-mediated response. The humoral response is mediated by antibodies, while the cell-mediated response involves cells classified as lymphocytes. Recent anticancer and antiviral strategies have focused on mobilizing the host immune system as a means of anticancer or antiviral treatment or therapy.

The immune system functions in three phases to protect the host from foreign bodies: the cognitive phase, the activation phase, and the effector phase. In the cognitive phase, the immune system recognizes and signals the presence of a foreign antigen or invader in the body. The foreign antigen can be, for example, a cell surface marker from a neoplastic cell or a viral protein. Once the system is aware of an invading body, antigen specific cells of the immune system proliferate and differentiate in response to the invader-triggered signals. The last stage is the effector stage in which the effector cells of the immune system respond to and neutralize the detected invader.

An array of effector cells implements an immune response to an invader. One type of effector cell, the B cell, generates antibodies targeted against foreign antigens encountered by the host. In combination with the complement system, antibodies direct the destruction of cells or organisms bearing the targeted antigen. Another type of effector cell is the natural killer cell (NK cell), a type of lymphocyte having the capacity to spontaneously recognize and destroy a variety of virus infected cells as well as malignant cell types. The method used by NK cells to recognize target cells is poorly understood.

Another type of effector cell, the T cell, has members classified into three subcategories, each playing a different role in the immune response. Helper T cells secrete cytokines which stimulate the proliferation of other cells necessary for mounting an effective immune response, while suppressor T cells down-regulate the immune response. A third category of T cell, the cytotoxic T cell (CTL), is capable of directly lysing a targeted cell presenting a foreign antigen on its surface.

The Major Histocompatibility Complex and T Cell Target Recognition

T cells are antigen-specific immune cells that function in response to specific antigen signals. B lymphocytes and the antibodies they produce are also antigen-specific entities. However, unlike B lymphocytes, T cells do not respond to antigens in a free or soluble form. For a T cell to respond to an antigen, it requires the antigen to be processed to peptides which are then bound to a presenting structure encoded in the major histocompatibility complex (MHC). This requirement is called "MHC restriction" and it is the mechanism by which T cells differentiate "self" from "non-self" cells. If an antigen is not displayed by a recognizable MHC molecule, the T cell will not recognize and act on the antigen signal. T cells specific for a peptide bound to a

recognizable MHC molecule bind to these MHC-peptide complexes and proceed to the next stages of the immune response.

There are two types of MHC, class I MHC and class II MHC. T Helper cells ($CD4^+$) predominately interact with class II MHC proteins while cytolytic T cells ($CD8^+$) predominately interact with class I MHC proteins. Both classes of MHC protein are transmembrane proteins with a majority of their structure on the external surface of the cell. Additionally, both classes of MHC proteins have a peptide binding cleft on their external portions. It is in this cleft that small fragments of proteins, endogenous or foreign, are bound and presented to the extracellular environment.

Cells called "professional antigen presenting cells" (pAPCs) display antigens to T cells using the MHC proteins but additionally express various co-stimulatory molecules depending on the particular state of differentiation/activation of the pAPC. When T cells, specific for the peptide bound to a recognizable MHC protein, bind to these MHC-peptide complexes on pAPCs, the specific co-stimulatory molecules that act upon the T cell direct the path of differentiation/activation taken by the T cell. That is, the co-stimulation molecules affect how the T cell will act on antigenic signals in future encounters as it proceeds to the next stages of the immune response.

As discussed above, neoplastic cells are largely ignored by the immune system. A great deal of effort is now being expended in an attempt to harness a host's immune system to aid in combating the presence of neoplastic cells in a host. One such area of research involves the formulation of anticancer vaccines.

Anticancer Vaccines

Among the various weapons available to an oncologist in the battle against cancer is the immune system of the patient. Work has been done in various attempts to cause the immune system to combat cancer or neoplastic diseases. Unfortunately, the results to date have been largely disappointing. One area of particular interest involves the generation and use of anticancer vaccines.

To generate a vaccine or other immunogenic composition, it is necessary to introduce to a subject an antigen or epitope against which an immune response may be mounted. Although neoplastic cells are derived from and therefore are substantially identical to normal cells on a genetic level, many neoplastic cells are known to present tumor-associated antigens (TuAAs). In theory, these antigens could be used by a subject's immune system to recognize these antigens and attack the neoplastic cells. In reality, however, neoplastic cells generally appear to be ignored by the host's immune system.

A number of different strategies have been developed in an attempt to generate vaccines with activity against neoplastic cells. These strategies include the use of tumor-associated antigens

as immunogens. For example, U.S. Patent No. 5,993,828, describes a method for producing an immune response against a particular subunit of the Urinary Tumor Associated Antigen by administering to a subject an effective dose of a composition comprising inactivated tumor cells having the Urinary Tumor Associated Antigen on the cell surface and at least one tumor associated antigen selected from the group consisting of GM-2, GD-2, Fetal Antigen and Melanoma Associated Antigen. Accordingly, this patent describes using whole, inactivated tumor cells as the immunogen in an anticancer vaccine.

Another strategy used with anticancer vaccines involves administering a composition containing isolated tumor antigens. In one approach, MAGE-A1 antigenic peptides were used as an immunogen. (See Chaux, P., *et al.*, "Identification of Five MAGE-A1 Epitopes Recognized by Cytolytic T Lymphocytes Obtained by *In Vitro* Stimulation with Dendritic Cells Transduced with MAGE-A1," J. Immunol., 163(5):2928-2936 (1999)). There have been several therapeutic trials using MAGE-A1 peptides for vaccination, although the effectiveness of the vaccination regimes was limited. The results of some of these trials are discussed in Vose, J.M., "Tumor Antigens Recognized by T Lymphocytes," 10th European Cancer Conference, Day 2, Sept. 14, 1999.

In another example of tumor associated antigens used as vaccines, Scheinberg, *et al.* treated 12 chronic myelogenous leukemia (CML) patients already receiving interferon (IFN) or hydroxyurea with 5 injections of class I-associated bcr-abl peptides with a helper peptide plus the adjuvant QS-21. Scheinberg, D.A., *et al.*, "BCR-ABL Breakpoint Derived Oncogene Fusion Peptide Vaccines Generate Specific Immune Responses in Patients with Chronic Myelogenous Leukemia (CML) [Abstract 1665], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999). Proliferative and delayed type hypersensitivity (DTH) T cell responses indicative of T-helper activity were elicited, but no cytolytic killer T cell activity was observed within the fresh blood samples.

Additional examples of attempts to identify TuAAs for use as vaccines are seen in the recent work of Cebon, *et al.* and Scheibenbogen, *et al.* Cebon, *et al.* immunized patients with metastatic melanoma using intradermally administered MART-1₂₆₋₃₅ peptide with IL-12 in increasing doses given either subcutaneously or intravenously. Of the first 15 patients, 1 complete remission, 1 partial remission, and 1 mixed response were noted. Immune assays for T cell generation included DTH, which was seen in patients with or without IL-12. Positive CTL assays were seen in patients with evidence of clinical benefit, but not in patients without tumor regression. Cebon, *et al.*, "Phase I Studies of Immunization with Melan-A and IL-12 in HLA A2+ Positive Patients with Stage III and IV Malignant Melanoma," [Abstract 1671], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999).

Scheibenbogen, *et al.* immunized 18 patients with 4 HLA class I restricted tyrosinase peptides, 16 with metastatic melanoma and 2 adjuvant patients. Scheibenbogen, *et al.*,

“Vaccination with Tyrosinase peptides and GM-CSF in Metastatic Melanoma: a Phase II Trial,” [Abstract 1680], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999). Increased CTL activity was observed in 4/15 patients, 2 adjuvant patients, and 2 patients with evidence of tumor regression. As in the trial by Cebon, *et al.*, patients with progressive disease did not show boosted immunity. In spite of the various efforts expended to date to generate efficacious anticancer vaccines, no such composition has yet been developed.

Antiviral Vaccines

Vaccine strategies to protect against viral diseases have had many successes. Perhaps the most notable of these is the progress that has been made against the disease small pox, which has been driven to extinction. The success of the polio vaccine is of a similar magnitude.

Viral vaccines can be grouped into three classifications: live attenuated virus vaccines, such as vaccinia for small pox, the Sabin poliovirus vaccine, and measles mumps and rubella; whole killed or inactivated virus vaccines, such as the Salk poliovirus vaccine, hepatitis A virus vaccine and the typical influenza virus vaccines; and subunit vaccines, such as hepatitis B. Due to their lack of a complete viral genome, subunit vaccines offer a greater degree of safety than those based on whole viruses.

The paradigm of a successful subunit vaccine is the recombinant hepatitis B vaccine based on the viruses envelope protein. Despite much academic interest in pushing the reductionist subunit concept beyond single proteins to individual epitopes, the efforts have yet to bear much fruit. Viral vaccine research has also concentrated on the induction of an antibody response although cellular responses also occur. However, many of the subunit formulations are particularly poor at generating a CTL response.

Summary of the Invention

Previous methods of priming professional antigen presenting cells (pAPCs) to display target cell epitopes have relied simply on causing the pAPCs to express target-associated antigens (TAAs), or epitopes of those antigens which are thought to have a high affinity for MHC I molecules. However, the proteasomal processing of such antigens results in presentation of epitopes on the pAPC that do not correspond to the epitopes present on the target cells.

Using the knowledge that an effective cellular immune response requires that pAPCs present the same epitope that is presented by the target cells, the present invention provides epitopes that have a high affinity for MHC I, and that correspond to the processing specificity of the housekeeping proteasome, which is active in peripheral cells. These epitopes thus correspond to those presented on target cells. The use of such epitopes in compositions, such as vaccines and other immunogenic compositions (including pharmaceutical and immunotherapeutic compositions) can activate the cellular immune response to recognize the correctly processed TAA and can result in removal of target cells that present such epitopes. In some embodiments, the housekeeping

epitopes provided herein can be used in combination with immune epitopes, generating a cellular immune response that is competent to attack target cells both before and after interferon induction. In other embodiments the epitopes are useful in the diagnosis and monitoring of the target-associated disease and in the generation of immunological reagents for such purposes.

5 Embodiments of the invention relate to isolated epitopes, antigens and/or polypeptides. The isolated antigens and/or polypeptides can include the epitopes. Preferred embodiments include an epitope or antigen having the sequence as disclosed in Tables 1A or 1B. Other embodiments can include an epitope cluster comprising a polypeptide from Tables 1A or 1B. Further, embodiments include a polypeptide having substantial similarity to the already mentioned epitopes,
10 polypeptides, antigens, or clusters. Other preferred embodiments include a polypeptide having functional similarity to any of the above. Still further embodiments relate to a nucleic acid encoding the polypeptide of any of the epitopes, clusters, antigens, and polypeptides from Tables 1A or 1B and mentioned herein.

 For purposes of the following summary and discussion of other embodiments of the
15 invention, reference to "the epitope," "the epitopes," or "epitope from Tables 1A or 1B" may include without limitation to all of the foregoing forms of the epitope including an epitope with the sequence set forth in the Tables or elsewhere herein, a cluster comprising such an epitope or epitopes, a polypeptide having substantial or functional similarity to those epitopes or clusters, and the like.

20 The polypeptide or epitope can be immunologically active. The polypeptide comprising the epitope can be less than about 30 amino acids in length, more preferably, the polypeptide is 8 to 10 amino acids in length, for example. Substantial or functional similarity can include addition of at least one amino acid, for example, and the at least one additional amino acid can be at an N-terminus of the polypeptide. The substantial or functional similarity can include a substitution of at
25 least one amino acid.

 The epitope, cluster, or polypeptide comprising the same can have affinity to an HLA-A2 molecule. The affinity can be determined by an assay of binding, by an assay of restriction of epitope recognition, by a prediction algorithm, and the like. The epitope, cluster, or polypeptide comprising the same can have affinity to an HLA-B7, HLA-B51 molecule, and the like.

30 In preferred embodiments the polypeptide can be a housekeeping epitope. The epitope or polypeptide can correspond to an epitope displayed on a tumor cell, to an epitope displayed on a neovasculature cell, and the like. The epitope or polypeptide can be an immune epitope. The epitope, cluster and/or polypeptide can be a nucleic acid. The epitope, cluster and/or polypeptide can be encoded by a nucleic acid.

35 Other embodiments relate to compositions, including pharmaceutical or immunogenic compositions comprising the polypeptides, including an epitope from Tables 1A or 1B, a cluster, or

a polypeptide comprising the same, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like. The adjuvant can be a polynucleotide. The polynucleotide can include a dinucleotide, which can be CpG, for example. The adjuvant can be encoded by a polynucleotide. The adjuvant can be a cytokine and the cytokine can be, for example, GM-CSF.

5 The compositions can further include a professional antigen-presenting cell (pAPC). The pAPC can be a dendritic cell, for example. The composition can further include a second epitope. The second epitope can be a polypeptide, a nucleic acid, a housekeeping epitope, an immune epitope, and the like.

10 Still further embodiments relate to compositions, including pharmaceutical and immunogenic compositions that include any of the nucleic acids discussed herein, including those that encode polypeptides that comprise epitopes or antigens from Tables 1A or 1B. Such compositions can include a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

15 Other embodiments relate to recombinant constructs that include such a nucleic acid as described herein, including those that encode polypeptides that comprise epitopes or antigens from Tables 1A or 1B. The constructs can further include a plasmid, a viral vector, an artificial chromosome, and the like. The construct can further include a sequence encoding at least one feature, such as for example, a second epitope, an IRES, an ISS, an NIS, a ubiquitin, and the like.

20 Further embodiments relate to purified antibodies that specifically bind to at least one of the epitopes in Tables 1A or 1B. Other embodiments relate to purified antibodies that specifically bind to a peptide-MHC protein complex comprising an epitope disclosed in Tables 1A or 1B or any other suitable epitope. The antibody from any embodiment can be a monoclonal antibody or a polyclonal antibody.

25 Still other embodiments relate to multimeric MHC-peptide complexes that include an epitope, such as, for example, an epitope disclosed in Tables 1A or 1B. Also, contemplated are antibodies specific for the complexes.

30 Embodiments relate to isolated T cells expressing a T cell receptor specific for an MHC-peptide complex. The complex can include an epitope, such as, for example, an epitope disclosed in Tables 1A or 1B. The T cell can be produced by an *in vitro* immunization and can be isolated from an immunized animal. Embodiments relate to T cell clones, including cloned T cells, such as those discussed above. Embodiments also relate to polyclonal population of T cells. Such populations can include a T cell, as described above, for example.

35 Still further embodiments relate to compositions, including pharmaceutical and immunogenic compositions that include a T cell, such as those described above, for example, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Embodiments of the invention relate to isolated protein molecules comprising the binding domain of a T cell receptor specific for an MHC-peptide complex. The complex can include an epitope as disclosed in Tables 1A or 1B. The protein can be multivalent. Other embodiments relate to isolated nucleic acids encoding such proteins. Still further embodiments relate to recombinant constructs that include such nucleic acids.

Other embodiments of the invention relate to host cells expressing a recombinant construct as described above and elsewhere herein. The host cells can include constructs encoding an epitope, a cluster or a polypeptide comprising said epitope or said cluster. The epitope or epitope cluster can be one or more of those disclosed in Tables 1A or 1B, for example, and as otherwise defined. The host cell can be a dendritic cell, macrophage, tumor cell, tumor-derived cell, a bacterium, fungus, protozoan, and the like. Embodiments also relate to compositions, including pharmaceutical and immunogenic compositions that include a host cell, such as those discussed herein, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Still other embodiments relate to compositions including immunogenic compositions, such as for example, vaccines or immunotherapeutic compositions. The compositions can include at least one component, such as, for example, an epitope disclosed in Tables 1A or 1B or otherwise described herein; a cluster that includes such an epitope, an antigen or polypeptide that includes such an epitope; a composition as described above and herein; a construct as described above and herein, a T cell, a construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex and compositions including the same, a host cell as described above and herein, and compositions comprising the same.

Further embodiments relate to methods of treating an animal. The methods can include administering to an animal a composition, including a pharmaceutical or an immunogenic composition, such as, a vaccine or immunotherapeutic composition, including those disclosed above and herein. The administering step can include a mode of delivery, such as, for example, transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, mucosal, aerosol inhalation, instillation, and the like. The method can further include a step of assaying to determine a characteristic indicative of a state of a target cell or target cells. The method can include a first assaying step and a second assaying step, wherein the first assaying step precedes the administering step, and wherein the second assaying step follows the administering step. The method can further include a step of comparing the characteristic determined in the first assaying step with the characteristic determined in the second assaying step to obtain a result. The result can be for example, evidence of an immune response, a diminution in number of target cells, a loss of mass or size of a tumor comprising target cells, a decrease in number or concentration of an intracellular parasite infecting target cells, and the like.

Embodiments relate to methods of evaluating immunogenicity of a composition, including a vaccine or an immunotherapeutic composition. The methods can include administering to an animal a vaccine or immunotherapeutic, such as those described above and elsewhere herein, and evaluating immunogenicity based on a characteristic of the animal. The animal can be MHC-transgenic.

Other embodiments relate to methods of evaluating immunogenicity that include *in vitro* stimulation of a T cell with the vaccine or immunotherapeutic composition, such as those described above and elsewhere herein, and evaluating immunogenicity based on a characteristic of the T cell. The stimulation can be a primary stimulation.

Still further embodiments relate to methods of making a passive/adoptive immunotherapeutic. The methods can include combining a T cell or a host cell, such as those described above and elsewhere herein, with a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Other embodiments relate to methods of determining specific T cell frequency, and can include the step of contacting T cells with a MHC-peptide complex comprising an epitope disclosed in Tables 1A or 1B, or a complex comprising a cluster or antigen comprising such an epitope. The contacting step can include at least one feature, such as, for example, immunization, restimulation, detection, enumeration, and the like. The method can further include ELISPOT analysis, limiting dilution analysis, flow cytometry, *in situ* hybridization, the polymerase chain reaction, any combination thereof, and the like.

Embodiments relate to methods of evaluating immunologic response. The methods can include the above-described methods of determining specific T cell frequency carried out prior to and subsequent to an immunization step.

Other embodiments relate to methods of evaluating immunologic response. The methods can include determining frequency, cytokine production, or cytolytic activity of T cells, prior to and subsequent to a step of stimulation with MHC-peptide complexes comprising an epitope, such as, for example an epitope from Tables 1A or 1B, a cluster or a polypeptide comprising such an epitope.

Further embodiments relate to methods of diagnosing a disease. The methods can include contacting a subject tissue with at least one component, including, for example, a T cell, a host cell, an antibody, a protein, including those described above and elsewhere herein; and diagnosing the disease based on a characteristic of the tissue or of the component. The contacting step can take place *in vivo* or *in vitro*, for example.

Still other embodiments relate to methods of making a composition, including for example, a vaccine. The methods can include combining at least one component. For example, the component can be an epitope, a composition, a construct, a T cell, a host cell; including any of

those described above and elsewhere herein, and the like, with a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Embodiments relate to computer readable media having recorded thereon the sequence of any one of SEQ ID NOS: 108-610, in a machine having a hardware or software that calculates the physical, biochemical, immunologic, molecular genetic properties of a molecule embodying said sequence, and the like.

Still other embodiments relate to methods of treating an animal. The methods can include combining the method of treating an animal that includes administering to the animal a vaccine or immunotherapeutic composition, such as described above and elsewhere herein, combined with at least one mode of treatment, including, for example, radiation therapy, chemotherapy, biochemotherapy, surgery, and the like.

Further embodiments relate to isolated polypeptides that include an epitope cluster. In preferred embodiments the cluster can be from a target-associated antigen having the sequence as disclosed in any one of Tables 68-73, wherein the amino acid sequence includes not more than about 80% of the amino acid sequence of the antigen.

Other embodiments relate to immunogenic compositions, including vaccines or immunotherapeutic products that include an isolated peptide as described above and elsewhere herein. Still other embodiments relate to isolated polynucleotides encoding a polypeptide as described above and elsewhere herein. Other embodiments relate vaccines or immunotherapeutic products that include these polynucleotides. The polynucleotide can be DNA, RNA, and the like.

Still further embodiments relate to kits comprising a delivery device and any of the embodiments mentioned above and elsewhere herein. The delivery device can be a catheter, a syringe, an internal or external pump, a reservoir, an inhaler, microinjector, a patch, and any other like device suitable for any route of delivery. As mentioned, the kit, in addition to the delivery device also includes any of the embodiments disclosed herein. For example, without limitations, the kit can include an isolated epitope, a polypeptide, a cluster, a nucleic acid, an antigen, a pharmaceutical composition that includes any of the foregoing, an antibody, a T cell, a T cell receptor, an epitope-MHC complex, a vaccine, an immunotherapeutic, and the like. The kit can also include items such as detailed instructions for use and any other like item.

Brief Description of the Drawings

Figure 1A-1C is a sequence alignment of NY-ESO-1 and several similar protein sequences.

Figure 2 graphically represents a plasmid vaccine backbone useful for delivering nucleic acid-encoded epitopes.

Figures 3A and 3B are FACS profiles showing results of HLA-A2 binding assays for tyrosinase₂₀₇₋₂₁₅ and tyrosinase₂₀₈₋₂₁₆.

Figure 3C shows cytolytic activity against a tyrosinase epitope by human CTL induced by *in vitro* immunization.

Figure 4 is a T=120 min. time point mass spectrum of the fragments produced by proteasomal cleavage of SSX-2₃₁₋₆₈.

5 Figure 5 shows a binding curve for HLA-A2:SSX-2₄₁₋₄₉ with controls.

Figure 6 shows specific lysis of SSX-2₄₁₋₄₉-pulsed targets by CTL from SSX-2₄₁₋₄₉-immunized HLA-A2 transgenic mice.

Figure 7A, B, and C show results of N-terminal pool sequencing of a T=60 min. time point aliquot of the PSMA₁₆₃₋₁₉₂ proteasomal digest.

10 Figure 8 shows binding curves for HLA-A2:PSMA₁₆₈₋₁₇₇ and HLA-A2:PSMA₂₈₈₋₂₉₇ with controls.

Figure 9 shows results of N-terminal pool sequencing of a T=60 min. time point aliquot of the PSMA₂₈₁₋₃₁₀ proteasomal digest.

15 Figure 10 shows binding curves for HLA-A2:PSMA₄₆₁₋₄₆₉, HLA-A2:PSMA₄₆₀₋₄₆₉, and HLA-A2:PSMA₆₆₃₋₆₇₁, with controls.

Figure 11 shows the results of a γ (gamma)-IFN-based ELISPOT assay detecting PSMA₄₆₃₋₄₇₁-reactive HLA-A1⁺ CD8⁺ T cells.

Figure 12 shows blocking of reactivity of the T cells used in figure 10 by anti-HLA-A1 mAb, demonstrating HLA-A1-restricted recognition.

20 Figure 13 shows a binding curve for HLA-A2:PSMA₆₆₃₋₆₇₁, with controls.

Figure 14 shows a binding curve for HLA-A2:PSMA₆₆₂₋₆₇₁, with controls.

Figure 15. Comparison of anti-peptide CTL responses following immunization with various doses of DNA by different routes of injection.

25 Figure 16. Growth of transplanted gp33 expressing tumor in mice immunized by i.ln. injection of gp33 epitope-expressing, or control, plasmid.

Figure 17. Amount of plasmid DNA detected by real-time PCR in injected or draining lymph nodes at various times after i.ln. of i.m. injection, respectively.

Figures 18-70 are proteasomal digestion maps depicting the mapping of mass spectrum peaks from the digest onto the sequence of the indicated substrate.

30 Detailed Description of the Preferred Embodiment

Definitions

Unless otherwise clear from the context of the use of a term herein, the following listed terms shall generally have the indicated meanings for purposes of this description.

35 PROFESSIONAL ANTIGEN-PRESENTING CELL (pAPC) – a cell that possesses T cell costimulatory molecules and is able to induce a T cell response. Well characterized pAPCs include dendritic cells, B cells, and macrophages.

PERIPHERAL CELL – a cell that is not a pAPC.

HOUSEKEEPING PROTEASOME – a proteasome normally active in peripheral cells, and generally not present or not strongly active in pAPCs.

IMMUNE PROTEASOME – a proteasome normally active in pAPCs; the immune
5 proteasome is also active in some peripheral cells in infected tissues.

EPITOPE – a molecule or substance capable of stimulating an immune response. In preferred embodiments, epitopes according to this definition include but are not necessarily limited to a polypeptide and a nucleic acid encoding a polypeptide, wherein the polypeptide is capable of stimulating an immune response. In other preferred embodiments, epitopes according to this
10 definition include but are not necessarily limited to peptides presented on the surface of cells, the peptides being non-covalently bound to the binding cleft of class I MHC, such that they can interact with T cell receptors (TCR). Epitopes presented by class I MHC may be in immature or mature form. “Mature” refers to an MHC epitope in distinction to any precursor (“immature”) that may include or consist essentially of a housekeeping epitope, but also includes other sequences in a
15 primary translation product that are removed by processing, including without limitation, alone or in any combination proteasomal digestion, N-terminal trimming, or the action of exogenous enzymatic activities. Thus, a mature epitope may be provided embedded in a somewhat longer polypeptide, the immunological potential of which is due, at least in part, to the embedded epitope; or in its ultimate form that can bind in the MHC binding cleft to be recognized by TCR,
20 respectively.

MHC EPITOPE – a polypeptide having a known or predicted binding affinity for a mammalian class I or class II major histocompatibility complex (MHC) molecule.

HOUSEKEEPING EPITOPE – In a preferred embodiment, a housekeeping epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which
25 housekeeping proteasomes are predominantly active. In another preferred embodiment, a housekeeping epitope is defined as a polypeptide containing a housekeeping epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, a housekeeping epitope is defined as a nucleic acid that encodes a housekeeping epitope according to the foregoing definitions.

IMMUNE EPITOPE – In a preferred embodiment, an immune epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which immune proteasomes are predominantly active. In another preferred embodiment, an immune epitope is defined as a polypeptide containing an immune epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, an immune
35 epitope is defined as a polypeptide including an epitope cluster sequence, having at least two polypeptide sequences having a known or predicted affinity for a class I MHC. In yet another

preferred embodiment, an immune epitope is defined as a nucleic acid that encodes an immune epitope according to any of the foregoing definitions.

TARGET CELL – a cell to be targeted by the vaccines and methods of the invention. Examples of target cells according to this definition include but are not necessarily limited to: a
5 neoplastic cell and a cell harboring an intracellular parasite, such as, for example, a virus, a bacterium, or a protozoan.

TARGET-ASSOCIATED ANTIGEN (TAA) – a protein or polypeptide present in a target cell.

TUMOR-ASSOCIATED ANTIGENS (TuAA) – a TAA, wherein the target cell is a
10 neoplastic cell.

HLA EPITOPE – a polypeptide having a known or predicted binding affinity for a human class I or class II HLA complex molecule.

ANTIBODY – a natural immunoglobulin (Ig), poly- or monoclonal, or any molecule composed in whole or in part of an Ig binding domain, whether derived biochemically or by use of
15 recombinant DNA. Examples include *inter alia*, F(ab), single chain Fv, and Ig variable region-phage coat protein fusions.

ENCODE – an open-ended term such that a nucleic acid encoding a particular amino acid sequence can consist of codons specifying that (poly)peptide, but can also comprise additional sequences either translatable, or for the control of transcription, translation, or replication, or to
20 facilitate manipulation of some host nucleic acid construct.

SUBSTANTIAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of the sequence. Nucleic acid sequences encoding the same amino acid sequence are substantially similar despite differences in degenerate positions or modest differences in length or composition of any non-coding regions.
25 Amino acid sequences differing only by conservative substitution or minor length variations are substantially similar. Additionally, amino acid sequences comprising housekeeping epitopes that differ in the number of N-terminal flanking residues, or immune epitopes and epitope clusters that differ in the number of flanking residues at either terminus, are substantially similar. Nucleic acids that encode substantially similar amino acid sequences are themselves also substantially similar.

30 FUNCTIONAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of a biological or biochemical property, although the sequences may not be substantially similar. For example, two nucleic acids can be useful as hybridization probes for the same sequence but encode differing amino acid sequences. Two peptides that induce cross-reactive CTL responses are functionally
35 similar even if they differ by non-conservative amino acid substitutions (and thus do not meet the substantial similarity definition). Pairs of antibodies, or TCRs, that recognize the same epitope can

be functionally similar to each other despite whatever structural differences exist. In testing for functional similarity of immunogenicity one would generally immunize with the "altered" antigen and test the ability of the elicited response (Ab, CTL, cytokine production, etc.) to recognize the target antigen. Accordingly, two sequences may be designed to differ in certain respects while
 5 retaining the same function. Such designed sequence variants are among the embodiments of the present invention.

VACCINE – this term is used to refer to those immunogenic compositions that are capable of eliciting prophylactic and/or therapeutic responses that prevent, cure, or ameliorate disease.

IMMUNOGENIC COMPOSITION - this term is used to refer to compositions capable of
 10 inducing an immune response, a reaction, an effect, and/or an event. In some embodiments, such responses, reactions, effects, and/or events can be induced *in vitro* or *in vivo*, for example. Included among these embodiments are the induction, activation, or expansion of cells involved in cell mediated immunity, for example. One example of such cells is cytotoxic T lymphocytes (CTLs). A vaccine is one type of immunogenic composition. Another example of such a
 15 composition is one that induces, activates, or expands CTLs *in vitro*. Further examples include pharmaceutical compositions and the like.

Table 1A. SEQ ID NOS.* including epitopes in Examples 1-7, 13, 14.

SEQ ID NO	IDENTITY	SEQUENCE
1	Tyr 207-216	FLPWHRLFL
2	Tyrosinase protein	Accession number**: P14679
3	SSX-2 protein	Accession number: NP_003138
4	PSMA protein	Accession number: NP_004467
5	Tyrosinase cDNA	Accession number: NM_000372
6	SSX-2 cDNA	Accession number: NM_003147
7	PSMA cDNA	Accession number: NM_004476
8	Tyr 207-215	FLPWHRLFL
9	Tyr 208-216	LPWHRLFL
10	SSX-2 31-68	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGF KATLP
11	SSX-2 32-40	FSKEEWEKM
12	SSX-2 39-47	KMKASEKIF
13	SSX-2 40-48	MKASEKIFY
14	SSX-2 39-48	KMKASEKIFY
15	SSX-2 41-49	KASEKIFYV
16	SSX-2 40-49	MKASEKIFYV
17	SSX-2 41-50	KASEKIFYVY
18	SSX-2 42-49	ASEKIFYVY
19	SSX-2 53-61	RKYEAMTKL
20	SSX-2 52-61	KRKYEAMTKL
21	SSX-2 54-63	KYEAMTKLGF
22	SSX-2 55-63	YEAMTKLGF
23	SSX-2 56-63	EAMTKLGF

SEQ ID NO	IDENTITY	SEQUENCE
24	HBV18-27	FLPSDYFPSV
25	HLA-B44 binder	AEMGKYSFY
26	SSX-1 41-49	KYSEKISYV
27	SSX-3 41-49	KVSEKIVYV
28	SSX-4 41-49	KSSEKIVYV
29	SSX-5 41-49	KASEKITYV
30	PSMA163-192	AFSPQGMPEGDLVYVNYARTEDFFKLERDM
31	PSMA 168-190	GMPEGDLVYVNYARTEDFFKLER
32	PSMA 169-177	MPEGDLVYV
33	PSMA 168-177	GMPEGDLVYV
34	PSMA 168-176	GMPEGDLVY
35	PSMA 167-176	QGMPEGDLVY
36	PSMA 169-176	MPEGDLVY
37	PSMA 171-179	EGDLVYVNY
38	PSMA 170-179	PEGDLVYVNY
39	PSMA 174-183	LVYVNYARTE
40	PSMA 177-185	VNYARTEF
41	PSMA 176-185	YVNYARTEF
42	PSMA 178-186	NYARTEFF
43	PSMA 179-186	YARTEFF
44	PSMA 181-189	RTEDFFKLE
45	PSMA 281-310	RGIAEAVGLPSIPVHPIGYYDAQKLEKMG
46	PSMA 283-307	IAEAVGLPSIPVHPIGYYDAQKLE
47	PSMA 289-297	LPSIPVHPI
48	PSMA 288-297	GLPSIPVHPI
49	PSMA 297-305	IGYYDAQKL
50	PSMA 296-305	PIGYYDAQKL
51	PSMA 291-299	SIPVHPIGY
52	PSMA 290-299	PSIPVHPIGY
53	PSMA 292-299	IPVHPIGY
54	PSMA 299-307	YYDAQKLE
55	PSMA454-481	SSIEGNYTLRVDCTPLMYSLVHLTKEL
56	PSMA 456-464	IEGNYTLRV
57	PSMA 455-464	SIEGNYTLRV
58	PSMA 457-464	EGNYTLRV
59	PSMA 461-469	TLRVDCTPL
60	PSMA 460-469	YTLRVDCTPL
61	PSMA 462-470	LRVDCTPLM
62	PSMA 463-471	RVDCTPLMY
63	PSMA 462-471	LRVDCTPLMY
64	PSMA653-687	FDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRPFY
65	PSMA 660-681	VLRMMNDQLMFLERAFIDPLGL
66	PSMA 663-671	MMNDQLMFL
67	PSMA 662-671	RMMNDQLMFL
68	PSMA 662-670	RMMNDQLMF
69	Tyr 1-17	MLLAVLYCLLWSFQ TSA
70	GP100 protein ²	Accession number: P40967
71	MAGE-1 protein	Accession number: P43355
72	MAGE-2 protein	Accession number: P43356

SEQ ID NO	IDENTITY	SEQUENCE
73	MAGE-3 protein	Accession number: P43357
74	NY-ESO-1 protein	Accession number: P78358
75	LAGE-1a protein	Accession number: CAA11116
76	LAGE-1b protein	Accession number: CAA11117
77	PRAME protein	Accession number: NP 006106
78	PSA protein	Accession number: P07288
79	PSCA protein	Accession number: O43653
80	GP100 cds	Accession number: U20093
81	MAGE-1 cds	Accession number: M77481
82	MAGE-2 cds	Accession number: L18920
83	MAGE-3 cds	Accession number: U03735
84	NY-ESO-1 cDNA	Accession number: U87459
85	PRAME cDNA	Accession number: NM 006115
86	PSA cDNA	Accession number: NM 001648
87	PSCA cDNA	Accession number: AF043498
88	CEA protein	Accession number: P06731
89	CEA cDNA	Accession number: NM 004363
90	Her2/Neu protein	Accession number: P04626
91	Her2/Neu cDNA	Accession number: M11730
92	SCP-1 protein	Accession number: Q15431
93	SCP-1 cDNA	Accession number: X95654
94	SSX-4 protein	Accession number: O60224
95	SSX-4 cDNA	Accession number: NM 005636
96	GAGE-1 protein	Accession number: Q13065
97	GAGE-1 cDNA	Accession number: U19142
98	Suvinin protein	Accession number: O15392
99	Survivin cDNA	Accession number: NM 001168
100	Melan-A protein	Accession number: Q16655
101	Melan-A cDNA	Accession number: U06452
102	BAGE protein	Accession number: Q13072
103	BAGE cDNA	Accession number: U19180
104	PSA 59-67	WVLTAAHCI
105	Glandular Kallikrein 1	Accession number: P06870
106	Elastase 2A	Accession number: P08217
107	Pancreatic elastase IIB	Accession number: NP_056933

Table 1B. SEQ ID NOS.* including epitopes in Examples 15-67.

SEQ ID NO	IDENTITY	SEQUENCE
108	Tyr 171-179	NIYDLFVWM
109	Tyr 173-182	YDLFVWMHY
110	Tyr 174-182	DLFVWMHY
111	Tyr 186-194	DALLGGSEI
112	Tyr 191-200	GSEIWRDIDF
113	Tyr 192-200	SEIWRDIDF
114	Tyr 193-201	EIWRDIDFA

SEQ ID NO	IDENTITY	SEQUENCE
115	Tyr 407-416	LQEVYPEANA
116	Tyr 409-418	EVYPEANAPI
117	Tyr 410-418	VYPEANAPI
118	Tyr 411-418	YPEANAPI
119	Tyr 411-420	YPEANAPIGH
120	Tyr 416-425	APIGHNRESY
121	Tyr 417-425	PIGHNRESY
122	Tyr 417-426	PIGHNRESYM
123	Tyr 416-425	APIGHNRESY
124	Tyr 417-425	PIGHNRESY
125	Tyr 423-430	ESYMPVFI
126	Tyr 423-432	ESYMPVFIPL
127	Tyr 424-432	SYMVPFIPL
128	Tyr 424-433	SYMVPFIPLY
129	Tyr 425-433	YMPVFIPLY
130	Tyr 426-434	MVPFIPLYR
131	Tyr 426-435	MVPFIPLYRN
132	Tyr 427-434	VPFIPLYR
133	Tyr 430-437	IPLYRNGD
134	Tyr 430-439	IPLYRNGDFF
135	Tyr 431-439	PLYRNGDFF
136	Tyr 431-440	PLYRNGDFFI
137	Tyr 434-443	RNGDFFISSK
138	Tyr 435-443	NGDFFISSK
139	Tyr 463-471	YIKSYLEQA
140	Tyr 466-474	SYLEQASRI
141	Tyr 469-478	EQASRIWSWL
142	Tyr 470-478	QASRIWSWL
143	Tyr 471-478	ASRIWSWL
144	Tyr 471-479	ASRIWSWLL
145	Tyr 473-481	RIWSWLLGA
146	CEA 92-100	GPAYSGREI
147	CEA 92-101	GPAYSGREII
148	CEA 93-100	PAYSGREI
149	CEA 93-101	PAYSGREII
150	CEA 93-102	PAYSGREIITY
151	CEA 94-102	AYSGREIITY
152	CEA 97-105	GREIITYPNA
153	CEA 98-107	REIITYPNASL
154	CEA 99-107	EIITYPNASL
155	CEA 99-108	EIITYPNASLL
156	CEA 100-107	IITYPNASL
157	CEA 100-108	IITYPNASLL
158	CEA 100-109	IITYPNASLLI
159	CEA 102-109	YPNASLLI
160	CEA 107-116	LLIQNIQND
161	CEA 132-141	EEATGQFRVY
162	CEA 133-141	EATGQFRVY
163	CEA 141-149	YPELPKPSI

SEQ ID NO	IDENTITY	SEQUENCE
164	CEA 142-149	PELPKPSI
165	CEA 225-233	RSDSVILNV
166	CEA 225-234	RSDSVILNVL
167	CEA 226-234	SDSVILNVL
168	CEA 226-235	SDSVILNVLY
169	CEA 227-235	DSVILNVLY
170	CEA 233-242	VLYGPDAPTI
171	CEA 234-242	LYGPDAPTI
172	CEA 235-242	YGPDAPTI
173	CEA 236-245	GPDAPTISPL
174	CEA 237-245	PDAPTISPL
175	CEA 238-245	DAPTISPL
176	CEA 239-247	APTISPLNT
177	CEA 240-249	PTISPLNTSY
178	CEA 241-249	TISPLNTSY
179	CEA 240-249	PTISPLNTSY
180	CEA 241-249	TISPLNTSY
181	CEA 246-255	NTSYRSGENL
182	CEA 247-255	TSYRSGENL
183	CEA 248-255	SYRSGENL
184	CEA 248-257	SYRSGENLNL
185	CEA 249-257	YRSGENLNL
186	CEA 251-259	SGENLNLSC
187	CEA 253-262	ENLNLSCHAA
188	CEA 254-262	NLNLSCHAA
189	CEA 260-269	HAASNPPAQY
190	CEA 261-269	AASNPPAQY
191	CEA 264-273	NPPAQYSWFV
192	CEA 265-273	PPAQYSWFV
193	CEA 266-273	PAQYSWFV
194	CEA 272-280	FVNGTFQQS
195	CEA 310-319	RTTVTTITVY
196	CEA 311-319	TTVTTITVY
197	CEA 319-327	YAEPPKPFI
198	CEA 319-328	YAEPPKPFIT
199	CEA 320-327	AEPPKPFI
200	CEA 321-328	EPPKPFIT
201	CEA 321-329	EPPKPFITS
202	CEA 322-329	PPKPFITS
203	CEA 382-391	SVTRNDVGPY
204	CEA 383-391	VTRNDVGPY
205	CEA 389-397	GPYECGIQN
206	CEA 391-399	YECGIQNEL
207	CEA 394-402	GIQNELSVD
208	CEA 403-411	HSDPVILNV
209	CEA 403-412	HSDPVILNVL
210	CEA 404-412	SDPVILNVL
211	CEA 404-413	SDPVILNVLY
212	CEA 405-412	DPVILNVL

SEQ ID NO	IDENTITY	SEQUENCE
213	CEA 405-413	DPVILNVLY
214	CEA 408-417	ILNVLYGPDD
215	CEA 411-420	VLYGPDDPTI
216	CEA 412-420	LYGPDDPTI
217	CEA 413-420	YGPDDPTI
218	CEA 417-425	DPTISPSYT
219	CEA 418-427	PTISPSYTTY
220	CEA 419-427	TISPSYTTY
221	CEA 418-427	PTISPSYTTY
222	CEA 419-427	TISPSYTTY
223	CEA 419-428	TISPSYTYR
224	CEA 424-433	YTYRPGVNL
225	CEA 425-433	TYRPGVNL
226	CEA 426-433	YYRPGVNL
227	CEA 426-435	YYRPGVNL
228	CEA 427-435	YRPGVNL
229	CEA 428-435	RPGVNL
230	CEA 428-437	RPGVNL
231	CEA 430-438	GVNLSCH
232	CEA 431-440	VNLSCHAA
233	CEA 432-440	NLSCHAA
234	CEA 438-447	HAASNPPAQY
235	CEA 439-447	AASNPPAQY
236	CEA 442-451	NPPAQSWLI
237	CEA 443-451	PPAQSWLI
238	CEA 444-451	PAQSWLI
239	CEA 449-458	WLIDGNIQQH
240	CEA 450-458	LIDGNIQQH
241	CEA 450-459	LIDGNIQQHT
242	CEA 581-590	RSDPVTLDVL
243	CEA 582-590	SDPVTLDVL
244	CEA 582-591	SDPVTLDVLY
245	CEA 583-590	DPVTLDVL
246	CEA 583-591	DPVTLDVLY
247	CEA 588-597	DVLYGPDTP
248	CEA 589-597	VLYGPDTP
249	CEA 596-605	PIISPDPSSY
250	CEA 597-605	IISPDPSSY
251	CEA 597-606	IISPDPSSYL
252	CEA 599-606	SPPDPSSYL
253	CEA 600-608	PPDPSSYLSG
254	CEA 600-609	PPDPSSYLSGA
255	CEA 602-611	DSSYLSGANL
256	CEA 603-611	SSYLSGANL
257	CEA 604-613	SYLSGANL
258	CEA 605-613	YLSGANL
259	CEA 610-618	NLNLSCHSA
260	CEA 620-629	NPSQYSWRI
261	CEA 622-629	SPQYSWRI

SEQ ID NO	IDENTITY	SEQUENCE
262	CEA 627-635	WRINGIPQQ
263	CEA 628-636	RINGIPQOH
264	CEA 628-637	RINGIPQOHT
265	CEA 631-639	GIPQOHTQV
266	CEA 632-639	IPQOHTQV
267	CEA 644-653	KITPNNNGTY
268	CEA 645-653	ITPNNNGTY
269	CEA 647-656	PNNNGTYACF
270	CEA 648-656	NNNGTYACF
271	CEA 650-657	NGTYACFV
272	CEA 661-670	ATGRNNSIVK
273	CEA 662-670	TGRNNSIVK
274	CEA 664-672	RNNSIVKSI
275	CEA 666-674	NSIVKSITV
276	GAGE-1 7-16	STYRPRPRRY
277	GAGE-1 8-16	TYRPRPRRY
278	GAGE-1 10-18	RPRPRRYVE
279	GAGE-1 16-23	YVEPPEMI
280	GAGE-1 22-31	MIGPMRPEQF
281	GAGE-1 23-31	IGPMRPEQF
282	GAGE-1 24-31	GPMRPEQF
283	GAGE-1 105-114	KTPEEEMRSH
284	GAGE-1 106-115	TPEEEMRSHY
285	GAGE-1 107-115	PEEEMRSHY
286	GAGE-1 110-119	EMRSHYVAQT
287	GAGE-1 113-121	SHYVAQTGI
288	GAGE-1 115-124	YVAQTGILWL
289	GAGE-1 116-124	VAQTGILWL
290	GAGE-1 116-125	VAQTGILWLL
291	GAGE-1 117-125	AQTGILWLL
292	GAGE-1 118-126	QTGILWLLM
293	GAGE-1 118-127	QTGILWLLMN
294	GAGE-1 120-129	GILWLLMNNC
295	GAGE-1 121-129	ILWLLMNNC
296	GAGE-1 124-131	LLMNNCFL
297	GAGE-1 123-131	WLLMNNCFL
298	GAGE-1 122-130	LWLLMNNCF
299	GAGE-1 121-130	ILWLLMNNCF
300	GAGE-1 121-129	ILWLLMNNC
301	GAGE-1 120-129	GILWLLMNNC
302	GAGE-1 118-127	QTGILWLLMN
303	GAGE-1 118-126	QTGILWLLM
304	GAGE-1 117-125	AQTGILWLL
305	GAGE-1 116-125	VAQTGILWLL
306	GAGE-1 116-124	VAQTGILWL
307	GAGE-1 115-124	YVAQTGILWL
308	GAGE-1 113-121	SHYVAQTGI
309	MAGE-1 62-70	SAFPTTINF
310	MAGE-1 61-70	ASAFPTTINF

SEQ ID NO	IDENTITY	SEQUENCE
311	MAGE-1 60-68	GASAFPTTI
312	MAGE-1 57-66	SPQGASAFPT
313	MAGE-1 144-151	FGKASESL
314	MAGE-1 143-151	IFGKASESL
315	MAGE-1 142-151	EIFGKASESL
316	MAGE-1 142-149	EIFGKASE
317	MAGE-1 133-140	IKNYKHCF
318	MAGE-1 132-140	VIKNYKHCF
319	MAGE-1 131-140	SVIKNYKHCF
320	MAGE-1 132-139	VIKNYKHC
321	MAGE-1 131-139	SVIKNYKHC
322	MAGE-1 128-136	MLESVIKNY
323	MAGE-1 127-136	EMLESVIKNY
324	MAGE-1 126-134	AEMLESVIK
325	MAGE-2 274-283	GPRALIETSY
326	MAGE-2 275-283	PRALIETSY
327	MAGE-2 276-284	RALIETSYV
328	MAGE-2 277-286	ALIETSYVKV
329	MAGE-2 278-286	LIETSYVKV
330	MAGE-2 278-287	LIETSYVKVL
331	MAGE-2 279-287	IETSYVKVL
332	MAGE-2 280-289	ETSYVKVLHH
333	MAGE-2 282-291	SYVKVLHHTL
334	MAGE-2 283-291	YVKVLHHTL
335	MAGE-2 285-293	KVLHHTLKI
336	MAGE-2 303-311	PLHERALRE
337	MAGE-2 302-309	PPLHERAL
338	MAGE-2 301-309	YPPLHERAL
339	MAGE-2 300-309	SYPPLHERAL
340	MAGE-2 299-307	ISYPPLHER
341	MAGE-2 298-307	HISYPPLHER
342	MAGE-2 292-299	KIGGEPHI
343	MAGE-2 291-299	LKIGGEPHI
344	MAGE-2 290-299	TLKIGGEPHI
345	MAGE-3 303-311	PLHEWVLRE
346	MAGE-3 302-309	PPLHEWVL
347	MAGE-3 301-309	YPPLHEWVL
348	MAGE-3 301-308	YPPLHEWV
349	MAGE-3 300-308	SYPPLHEWV
350	MAGE-3 299-308	ISYPPLHEWV
351	MAGE-3 298-307	HISYPPLHEW
352	MAGE-3 293-301	ISGGPHISY
353	MAGE-3 292-301	KISGGPHISY
354	Melan-A 45-54	CWYCRRRNGY
355	Melan-A 46-54	WYCRRRNGY
356	Melan-A 47-55	YCRRRNGYR
357	Melan-A 49-57	RRRNGYRAL
358	Melan-A 51-60	RNGYRALMDK
359	Melan-A 52-60	NGYRALMDK

SEQ ID NO	IDENTITY	SEQUENCE
360	Melan-A 55-63	RALMDKSLH
361	Melan-A 56-63	ALMDKSLH
362	Melan-A 55-64	RALMDKSLHV
363	Melan-A 56-64	ALMDKSLHV
364	PRAME 275-284	YISPEKEEQY
365	PRAME 276-284	ISPEKEEQY
366	PRAME 277-285	SPEKEEQYI
367	PRAME 278-285	PEKEEQYI
368	PRAME 279-288	EKEEQYIAQF
369	PRAME 280-288	KEEQYIAQF
370	PRAME 283-292	QYIAQFTSQF
371	PRAME 284-292	YIAQFTSQF
372	PRAME 284-293	YIAQFTSQFL
373	PRAME 285-293	IAQFTSQFL
374	PRAME 286-295	AQFTSQFLSL
375	PRAME 287-295	QFTSQFLSL
376	PRAME 290-298	SQFLSLQCL
377	PRAME 439-448	VLYPVPLESY
378	PRAME 440-448	LYPVPLESY
379	PRAME 446-455	ESYEDIHGTI
380	PRAME 448-457	YEDIHGTIHL
381	PRAME 449-457	EDIHGTIHL
382	PRAME 451-460	IHGTIHLERL
383	PRAME 454-463	TLHLERLAYL
384	PRAME 455-463	LHLERLAYL
385	PRAME 456-463	HLERLAYL
386	PRAME 456-465	HLERLAYLHA
387	PRAME 458-467	ERLAYLHARL
388	PRAME 459-467	RLAYLHARL
389	PRAME 459-468	RLAYLHARLR
390	PRAME 460-467	LAYLHARL
391	PRAME 460-468	LAYLHARLR
392	PRAME 461-470	AYLHARLREL
393	PRAME 462-470	YLHARLREL
394	PRAME 462-471	YLHARLRELL
395	PRAME 463-471	LHARLRELL
396	PRAME 464-471	HARLRELL
397	PRAME 464-472	HARLRELLC
398	PRAME 469-478	ELLCELGRPS
399	PRAME 470-478	LLCELGRPS
400	PSA 144-153	QEPALGTTCY
401	PSA 145-153	EPALGTTCY
402	PSA 162-171	PEEFLTPKKL
403	PSA 163-171	EEFLTPKKL
404	PSA 165-173	FLTPKKLQC
405	PSA 165-174	FLTPKKLQCV
406	PSA 166-174	LTPKKLQCV
407	PSA 167-174	TPKKLQCV
408	PSA 167-175	TPKKLQCVD

SEQ ID NO	IDENTITY	SEQUENCE
409	PSA 170-179	KLQCVDLHVI
410	PSA 171-179	LQCVDLHVI
411	PSCA 73-81	DSQDYVVGK
412	PSCA 74-82	SQDYVVGKK
413	PSCA 74-83	SQDYVVGKKN
414	PSCA 76-84	DYYVGGKNI
415	PSCA 77-84	YVVGKKNI
416	PSCA 78-86	YVGGKNITC
417	PSCA 78-87	YVGGKNITCC
418	PSMA 381-390	WVFGGIDPQS
419	PSMA 385-394	GIDPQSGAAV
420	PSMA 386-394	IDPQSGAAV
421	PSMA 387-394	DPQSGAAV
422	PSMA 387-395	DPQSGAAVV
423	PSMA 387-396	DPQSGAAVVH
424	PSMA 388-396	PQSGAAVVH
425	PSMA 389-398	QSGAAVVHEI
426	PSMA 390-398	SGAAVVHEI
427	PSMA 391-398	GAADVHEI
428	PSMA 391-399	GAADVHEIV
429	PSMA 392-399	AAVVHEIV
430	PSMA 597-605	CRDYAVVLR
431	PSMA 598-607	RDYAVVLRKY
432	PSMA 599-607	DYAVVLRKY
433	PSMA 600-607	YAVVLRKY
434	PSMA 602-611	VVLRKYADKI
435	PSMA 603-611	VLRKYADKI
436	PSMA 603-612	VLRKYADKIY
437	PSMA 604-611	LRKYADKI
438	PSMA 604-612	LRKYADKIY
439	PSMA 605-614	RKYADKIYSI
440	PSMA 606-614	KYADKIYSI
441	PSMA 607-614	YADKIYSI
442	PSMA 616-625	MKHPQEMKTY
443	PSMA 617-625	KHPQEMKTY
444	PSMA 618-627	HPQEMKTYSV
445	SCP-1 62-71	IDSDPALQKV
446	SCP-1 63-71	DSDPALQKV
447	SCP-1 67-76	ALQKVNFLPV
448	SCP-1 70-78	KVNFLPVLE
449	SCP-1 71-80	VNFLPVLEQV
450	SCP-1 72-80	NFLPVLEQV
451	SCP-1 75-84	PVLEQVGNSD
452	SCP-1 76-84	VLEQVGNSD
453	SCP-1 202-210	YEREETRQV
454	SCP-1 202-211	YEREETRQVY
455	SCP-1 203-211	EREETRQVY
456	SCP-1 203-212	EREETRQVYM
457	SCP-1 204-212	REETRQVYM

SEQ ID NO	IDENTITY	SEQUENCE
458	SCP-1 211-220	YMDLNSNIEK
459	SCP-1 213-221	DLNSNIEKM
460	SCP-1 216-226	SNIEKMITAF
461	SCP-1 217-225	NIEKMITAF
462	SCP-1 218-225	IEKMITAF
463	SCP-1 397-406	RLENYEDQLI
464	SCP-1 398-406	LENYEDQLI
465	SCP-1 398-407	LENYEDQLII
466	SCP-1 399-407	ENYEDQLII
467	SCP-1 399-408	ENYEDQLIIL
468	SCP-1 400-408	NYEDQLIIL
469	SCP-1 400-409	NYEDQLIILT
470	SCP-1 401-409	YEDQLIILT
471	SCP-1 401-410	YEDQLIILTM
472	SCP-1 402-410	EDQLIILTM
473	SCP-1 406-415	IILTMELQKT
474	SCP-1 407-415	ILTMELQKT
475	SCP-1 424-432	KLTNNKEVE
476	SCP-1 424-433	KLTNNKEVEL
477	SCP-1 425-433	LTNNKEVEL
478	SCP-1 429-438	KEVELEELKK
479	SCP-1 430-438	EVELEELKK
480	SCP-1 430-439	EVELEELKKV
481	SCP-1 431-439	VELEELKKV
482	SCP-1 530-539	ETSDMTLELK
483	SCP-1 531-539	TSDMTLELK
484	SCP-1 548-556	NKKQEERML
485	SCP-1 553-562	ERMLTQIENL
486	SCP-1 554-562	RMLTQIENL
487	SCP-1 555-562	MLTQIENL
488	SCP-1 555-564	MLTQIENLQE
489	SCP-1 560-569	ENLQETETQL
490	SCP-1 561-569	NLQETETQL
491	SCP-1 561-570	NLQETETQLR
492	SCP-1 567-576	TQLRNELEYV
493	SCP-1 568-576	QLRNELEYV
494	SCP-1 571-580	NELEYVREEL
495	SCP-1 572-580	ELEYVREEL
496	SCP-1 573-580	LEYVREEL
497	SCP-1 574-583	EYVREELKQK
498	SCP-1 575-583	YVREELKQK
499	SCP-1 675-684	LLEEVEKAKV
500	SCP-1 676-684	LEEVEKAKV
501	SCP-1 676-685	LEEVEKAKVI
502	SCP-1 677-685	EEVEKAKVI
503	SCP-1 681-690	KAKVIADAV
504	SCP-1 683-692	KVIADAVKL
505	SCP-1 684-692	VIADAVKL
506	SCP-1 685-692	IADAVKL

SEQ ID NO	IDENTITY	SEQUENCE
507	SCP-1 694-702	KEIDKRCQH
508	SCP-1 694-703	KEIDKRCQHK
509	SCP-1 695-703	EIDKRCQHK
510	SCP-1 695-704	EIDKRCQHKI
511	SCP-1 696-704	IDKRCQHKI
512	SCP-1 697-704	DKRCQHKI
513	SCP-1 698-706	KRCQHKIAE
514	SCP-1 698-707	KRCQHKIAEM
515	SCP-1 699-707	RCQHKIAEM
516	SCP-1 701-710	QHKAEMVAL
517	SCP-1 702-710	HKIAEMVAL
518	SCP-1 703-710	KIAEMVAL
519	SCP-1 737-746	QEQSSLRASL
520	SCP-1 738-746	EQSSLRASL
521	SCP-1 739-746	QSSLRASL
522	SCP-1 741-750	SLRASLEIEL
523	SCP-1 742-750	LRASLEIEL
524	SCP-1 743-750	RASLEIEL
525	SCP-1 744-753	ASLEIELSNL
526	SCP-1 745-753	SLEIELSNL
527	SCP-1 745-754	SLEIELSNLK
528	SCP-1 746-754	LEIELSNLK
529	SCP-1 747-755	EIELSNLKA
530	SCP-1 749-758	ELSNLKAELL
531	SCP-1 750-758	LSNLKAELL
532	SCP-1 751-760	SNLKAELLSV
533	SCP-1 752-760	NLKAELLSV
534	SCP-1 752-761	NLKAELLSVK
535	SCP-1 753-761	LKAELLSVK
536	SCP-1 753-762	LKAELLSVKK
537	SCP-1 754-762	KAELLSVKK
538	SCP-1 755-763	AELLSVKKQ
539	SCP-1 787-796	EKKDKKTQTF
540	SCP-1 788-796	KKDKKTQTF
541	SCP-1 789-796	KDKKTQTF
542	SCP-1 797-806	LLETPDIYWK
543	SCP-1 798-806	LETPDIYWK
544	SCP-1 798-807	LETPDIYWKL
545	SCP-1 799-807	ETPDIYWKL
546	SCP-1 800-807	TPDIYWKL
547	SCP-1 809-817	SKAVPSQTV
548	SCP-1 810-817	KAVPSQTV
549	SCP-1 812-821	VPSQTVSRNF
550	SCP-1 815-824	QTVSRNFTSV
551	SCP-1 816-824	TVSRNFTSV
552	SCP-1 816-825	TVSRNFTSVD
553	SCP-1 823-832	SVDHGISKDK
554	SCP-1 829-838	SKDKRDYLWT
555	SCP-1 832-840	KRDYLTWSA

SEQ ID NO	IDENTITY	SEQUENCE
556	SCP-1 832-841	KRDYLWTS AK
557	SCP-1 833-841	RDYLWTS AK
558	SCP-1 835-843	YLWTS AKNT
559	SCP-1 835-844	YLWTS AKNTL
560	SCP-1 837-844	WTS AKNTL
561	SCP-1 841-850	KNTLSTPLPK
562	SCP-1 842-850	NTLSTPLPK
563	SCP-1 832-840	KRDYLWTS A
564	SCP-1 832-841	KRDYLWTS AK
565	SCP-1 833-841	RDYLWTS AK
566	SCP-1 835-843	YLWTS AKNT
567	SCP-1 839-846	SAKNTLST
568	SCP-1 841-850	KNTLSTPLPK
569	SCP-1 842-850	NTLSTPLPK
570	SCP-1 843-852	TLSTPLPKAY
571	SCP-1 844-852	LSTPLPKAY
572	SSX-2 5-12	DAFARRPT
573	SSX-2 7-15	FARRPTVGA
574	SSX-2 8-17	ARRPTVGAQI
575	SSX-2 9-17	RRPTVGAQI
576	SSX-2 10-17	RPTVGAQI
577	SSX-2 13-21	VGAQIPEKI
578	SSX-2 14-21	GAQIPEKI
579	SSX-2 15-24	AQIPEKIQKA
580	SSX-2 16-24	QIPEKIQKA
581	SSX-2 16-25	QIPEKIQKAF
582	SSX-2 17-24	IPEKIQKA
583	SSX-2 17-25	IPEKIQKAF
584	SSX-2 18-25	PEKIQKAF
585	Survivin 116-124	ETNNKKKEF
586	Survivin 117-124	TNNKKKEF
587	Survivin 122-131	KEFEETAKKV
588	Survivin 123-131	EFEETAKKV
589	Survivin 127-134	TAKKVRRRA
590	Survivin 126-134	ETAKKVRRRA
591	Survivin 128-136	AKKVRRRAIE
592	Survivin 129-138	KKVRRRAIEQL
593	Survivin 130-138	KVRRRAIEQL
594	Survivin 130-139	KVRRRAIEQLA
595	Survivin 131-138	VRRAIEQL
596	BAGE 24-31	SPVVS WRL
597	BAGE 21-29	KEESP VVS W
598	BAGE 19-27	LMKEESP VV
599	BAGE 18-27	RLMKEESP VV
600	BAGE 18-26	RLMKEESP V
601	BAGE 14-22	LLQARLMKE
602	BAGE 13-22	QLLQARLMKE
603	Survivin 13-28	FLKDHRISTFKNWPFL
604	Survivin 79-111	KHSSGCAFLSVKKQFEELTLGEFLKLDRE RAKN

SEQ ID NO	IDENTITY	SEQUENCE
605	Survivin 130-141	KVRRRAIEQLAAM
606	GAGE-1 116-133	VAQTGILWLLMNNCFNL
607	BAGE 7-17	FLALSAQLLQA
608	BAGE 18-27	RLMKEESPVV
609	BAGE 2-27	AARAVFLALSAQLLQARLMKEESPVV
610	BAGE 30-39	RLEPEDGTAL

*Any of SEQ ID NOS. 108-602 can be useful as epitopes in any of the various embodiments of the invention. Any of SEQ ID NOS. 603-610 can be useful as sequences containing epitopes or epitope clusters, as described in various embodiments of the invention.

**All accession numbers used here and throughout can be accessed through the NCBI databases, for example, through the Entrez seek and retrieval system on the world wide web.

Note that the following discussion sets forth the inventors' understanding of the operation of the invention. However, it is not intended that this discussion limit the patent to any particular theory of operation not set forth in the claims.

In pursuing the development of epitope vaccines others have generated lists of predicted epitopes based on MHC binding motifs. Such peptides can be immunogenic, but may not correspond to any naturally produced antigenic fragment. Therefore, whole antigen will not elicit a similar response or sensitize a target cell to cytolysis by CTL. Therefore such lists do not differentiate between those sequences that can be useful as vaccines and those that cannot. Efforts to determine which of these predicted epitopes are in fact naturally produced have often relied on screening their reactivity with tumor infiltrating lymphocytes (TIL). However, TIL are strongly biased to recognize immune epitopes whereas tumors (and chronically infected cells) will generally present housekeeping epitopes. Thus, unless the epitope is produced by both the housekeeping and immuno- proteasomes, the target cell will generally not be recognized by CTL induced with TIL-identified epitopes. The epitopes of the present invention, in contrast, are generated by the action of a specified proteasome, indicating that they can be naturally produced, and enabling their appropriate use. The importance of the distinction between housekeeping and immune epitopes to vaccine design is more fully set forth in PCT publication WO 01/82963A2. The teachings and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

The epitopes of the invention include or encode polypeptide fragments of TAAs that are precursors or products of proteasomal cleavage by a housekeeping or immune proteasome, and that contain or consist of a sequence having a known or predicted affinity for at least one allele of MHC I. In some embodiments, the epitopes include or encode a polypeptide of about 6 to 25 amino acids in length, preferably about 7 to 20 amino acids in length, more preferably about 8 to 15 amino acids in length, and still more preferably 9 or 10 amino acids in length. However, it is understood that the polypeptides can be larger as long as N-terminal trimming can produce the MHC epitope or that

they do not contain sequences that cause the polypeptides to be directed away from the proteasome or to be destroyed by the proteasome. For immune epitopes, if the larger peptides do not contain such sequences, they can be processed in the pAPC by the immune proteasome. Housekeeping epitopes may also be embedded in longer sequences provided that the sequence is adapted to facilitate liberation of the epitope's C-terminus by action of the immunoproteasome. The foregoing discussion has assumed that processing of longer epitopes proceeds through action of the immunoproteasome of the pAPC. However, processing can also be accomplished through the contrivance of some other mechanism, such as providing an exogenous protease activity and a sequence adapted so that action of the protease liberates the MHC epitope. The sequences of these epitopes can be subjected to computer analysis in order to calculate physical, biochemical, immunologic, or molecular genetic properties such as mass, isoelectric point, predicted mobility in electrophoresis, predicted binding to other MHC molecules, melting temperature of nucleic acid probes, reverse translations, similarity or homology to other sequences, and the like.

In constructing the polynucleotides encoding the polypeptide epitopes of the invention, the gene sequence of the associated TAA can be used, or the polynucleotide can be assembled from any of the corresponding codons. For a 10 amino acid epitope this can constitute on the order of 10^6 different sequences, depending on the particular amino acid composition. While large, this is a distinct and readily definable set representing a miniscule fraction of the $>10^{18}$ possible polynucleotides of this length, and thus in some embodiments, equivalents of a particular sequence disclosed herein encompass such distinct and readily definable variations on the listed sequence. In choosing a particular one of these sequences to use in a vaccine, considerations such as codon usage, self-complementarity, restriction sites, chemical stability, etc. can be used as will be apparent to one skilled in the art.

The invention contemplates producing peptide epitopes. Specifically these epitopes are derived from the sequence of a TAA, and have known or predicted affinity for at least one allele of MHC I. Such epitopes are typically identical to those produced on target cells or pAPCs.

Compositions Containing Active Epitopes

Embodiments of the present invention provide polypeptide compositions, including vaccines, therapeutics, diagnostics, pharmacological and pharmaceutical compositions. The various compositions include newly identified epitopes of TAAs, as well as variants of these epitopes. Other embodiments of the invention provide polynucleotides encoding the polypeptide epitopes of the invention. The invention further provides vectors for expression of the polypeptide epitopes for purification. In addition, the invention provides vectors for the expression of the polypeptide epitopes in an APC for use as an anti-tumor vaccine. Any of the epitopes or antigens, or nucleic acids encoding the same, from Table 1 can be used. Other embodiments relate to methods of making and using the various compositions.

A general architecture for a class I MHC-binding epitope can be described, and has been reviewed more extensively in Madden, D.R. *Annu. Rev. Immunol.* 13:587-622, 1995. Much of the binding energy arises from main chain contacts between conserved residues in the MHC molecule and the N- and C-termini of the peptide. Additional main chain contacts are made but vary among MHC alleles. Sequence specificity is conferred by side chain contacts of so-called anchor residues with pockets that, again, vary among MHC alleles. Anchor residues can be divided into primary and secondary. Primary anchor positions exhibit strong preferences for relatively well-defined sets of amino acid residues. Secondary positions show weaker and/or less well-defined preferences that can often be better described in terms of less favored, rather than more favored, residues. Additionally, residues in some secondary anchor positions are not always positioned to contact the pocket on the MHC molecule at all. Thus, a subset of peptides exists that bind to a particular MHC molecule and have a side chain-pocket contact at the position in question and another subset exists that show binding to the same MHC molecule that does not depend on the conformation the peptide assumes in the peptide-binding groove of the MHC molecule. The C-terminal residue (P Ω ; omega) is preferably a primary anchor residue. For many of the better studied HLA molecules (e.g. A2, A68, B27, B7, B35, and B53) the second position (P2) is also an anchor residue. However, central anchor residues have also been observed including P3 and P5 in HLA-B8, as well as P5 and P Ω (omega)-3 in the murine MHC molecules H-2D^b and H-2K^b, respectively. Since more stable binding will generally improve immunogenicity, anchor residues are preferably conserved or optimized in the design of variants, regardless of their position.

Because the anchor residues are generally located near the ends of the epitope, the peptide can buckle upward out of the peptide-binding groove allowing some variation in length. Epitopes ranging from 8-11 amino acids have been found for HLA-A68, and up to 13 amino acids for HLA-A2. In addition to length variation between the anchor positions, single residue truncations and extensions have been reported and the N- and C-termini, respectively. Of the non-anchor residues, some point up out of the groove, making no contact with the MHC molecule but being available to contact the TCR, very often P1, P4, and P Ω (omega)-1 for HLA-A2. Others of the non-anchor residues can become interposed between the upper edges of the peptide-binding groove and the TCR, contacting both. The exact positioning of these side chain residues, and thus their effects on binding, MHC fine conformation, and ultimately immunogenicity, are highly sequence dependent. For an epitope to be highly immunogenic it must not only promote stable enough TCR binding for activation to occur, but the TCR must also have a high enough off-rate that multiple TCR molecules can interact sequentially with the same peptide-MHC complex (Kalergis, A.M. et al., *Nature Immunol.* 2:229-234, 2001). Thus, without further information about the ternary complex, both conservative and non-conservative substitutions at these positions merit consideration when designing variants.

The polypeptide epitope variants can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations. Variants can be derived from substitution, deletion or insertion of one or more amino acids as compared with the native sequence. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a threonine with a serine, for example. Such replacements are referred to as conservative amino acid replacements, and all appropriate conservative amino acid replacements are considered to be embodiments of one invention. Insertions or deletions can optionally be in the range of about 1 to 4, preferably 1 to 2, amino acids. It is generally preferable to maintain the "anchor positions" of the peptide which are responsible for binding to the MHC molecule in question. Indeed, immunogenicity of peptides can be improved in many cases by substituting more preferred residues at the anchor positions (Franco, et al., *Nature Immunology*, 1(2):145-150, 2000). Immunogenicity of a peptide can also often be improved by substituting bulkier amino acids for small amino acids found in non-anchor positions while maintaining sufficient cross-reactivity with the original epitope to constitute a useful vaccine. The variation allowed can be determined by routine insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the polypeptide epitope. Because the polypeptide epitope is often 9 amino acids, the substitutions preferably are made to the shortest active epitope, for example, an epitope of 9 amino acids.

Variants can also be made by adding any sequence onto the N-terminus of the polypeptide epitope variant. Such N-terminal additions can be from 1 amino acid up to at least 25 amino acids. Because peptide epitopes are often trimmed by N-terminal exopeptidases active in the pAPC, it is understood that variations in the added sequence can have no effect on the activity of the epitope. In preferred embodiments, the amino acid residues between the last upstream proteasomal cleavage site and the N-terminus of the MHC epitope do not include a proline residue. Serwold, T. et al., *Nature Immunol.* 2:644-651, 2001. Accordingly, effective epitopes can be generated from precursors larger than the preferred 9-mer class I motif.

Generally, peptides are useful to the extent that they correspond to epitopes actually displayed by MHC I on the surface of a target cell or a pACP. A single peptide can have varying affinities for different MHC molecules, binding some well, others adequately, and still others not appreciably (Table 2). MHC alleles have traditionally been grouped according to serologic reactivity which does not reflect the structure of the peptide-binding groove, which can differ among different alleles of the same type. Similarly, binding properties can be shared across types; groups based on shared binding properties have been termed supertypes. There are numerous alleles of MHC I in the human population; epitopes specific to certain alleles can be selected based on the genotype of the patient.

Table 2.

Predicted Binding of Tyrosinase₂₀₇₋₂₁₆ (SEQ ID NO. 1) to Various MHC types

MHC I type	*Half time of dissociation (min)
A1	0.05
A*0201	1311.
A*0205	50.4
A3	2.7
A*1101 (part of the A3 supertype)	0.012
A24	6.0
B7	4.0
B8	8.0
B14 (part of the B27 supertype)	60.0
B*2702	0.9
B*2705	30.0
B*3501 (part of the B7 supertype)	2.0
B*4403	0.1
B*5101 (part of the B7 supertype)	26.0
B*5102	55.0
B*5801	0.20
B60	0.40
B62	2.0

5 *HLA Peptide Binding Predictions (world wide web hypertext transfer protocol "access at bimas.dcrf.nih.gov/molbio/hla_bin").

10 In further embodiments of the invention, the epitope, as peptide or encoding polynucleotide, can be administered as a pharmaceutical composition, such as, for example, a vaccine or an immunogenic composition, alone or in combination with various adjuvants, carriers, or excipients. It should be noted that although the term vaccine may be used throughout the discussion herein, the concepts can be applied and used with any other pharmaceutical composition, including those mentioned herein. Particularly advantageous adjuvants include various cytokines and oligonucleotides containing immunostimulatory sequences (as set forth in greater detail in the co-pending applications referenced herein). Additionally the polynucleotide encoded epitope can be contained in a virus (e.g. *vaccinia* or adenovirus) or in a microbial host cell (e.g. *Salmonella* or *Listeria monocytogenes*) which is then used as a vector for the polynucleotide (Dietrich, G. et al. Nat. Biotech. 16:181-185, 1998). Alternatively a pAPC can be transformed, *ex vivo*, to express the epitope, or pulsed with peptide epitope, to be itself administered as a vaccine. To increase efficiency of these processes, the encoded epitope can be carried by a viral or bacterial vector, or complexed with a ligand of a receptor found on pAPC. Similarly the peptide epitope can be complexed with or conjugated to a pAPC ligand. A vaccine can be composed of more than a single epitope.

20 Particularly advantageous strategies for incorporating epitopes and/or epitope clusters, into a vaccine or pharmaceutical composition are disclosed in PCT Publication WO 01/82963 and U.S.

Patent Application No. 09/560,465 entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS," filed on April 28, 2000. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. Epitope clusters for use in connection with this invention
5 are disclosed in PCT Publication WO 01/82963 and U.S. Patent Application No. 09/561,571 entitled "EPITOPE CLUSTERS," filed on April 28, 2000. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

Preferred embodiments of the present invention are directed to vaccines and methods for
10 causing a pAPC or population of pAPCs to present housekeeping epitopes that correspond to the epitopes displayed on a particular target cell. Any of the epitopes or antigens in Table 1, can be used for example. In one embodiment, the housekeeping epitope is a TuAA epitope processed by the housekeeping proteasome of a particular tumor type. In another embodiment, the housekeeping epitope is a virus-associated epitope processed by the housekeeping proteasome of a cell infected
15 with a virus. This facilitates a specific T cell response to the target cells. Concurrent expression by the pAPCs of multiple epitopes, corresponding to different induction states (pre- and post-attack), can drive a CTL response effective against target cells as they display either housekeeping epitopes or immune epitopes.

By having both housekeeping and immune epitopes present on the pAPC, this embodiment
20 can optimize the cytotoxic T cell response to a target cell. With dual epitope expression, the pAPCs can continue to sustain a CTL response to the immune-type epitope when the tumor cell switches from the housekeeping proteasome to the immune proteasome with induction by IFN, which, for example, may be produced by tumor-infiltrating CTLs.

In a preferred embodiment, immunization of a patient is with a vaccine that includes a
25 housekeeping epitope. Many preferred TAAs are associated exclusively with a target cell, particularly in the case of infected cells. In another embodiment, many preferred TAAs are the result of deregulated gene expression in transformed cells, but are found also in tissues of the testis, ovaries and fetus. In another embodiment, useful TAAs are expressed at higher levels in the target cell than in other cells. In still other embodiments, TAAs are not differentially expressed in the
30 target cell compare to other cells, but are still useful since they are involved in a particular function of the cell and differentiate the target cell from most other peripheral cells; in such embodiments, healthy cells also displaying the TAA may be collaterally attacked by the induced T cell response, but such collateral damage is considered to be far preferable to the condition caused by the target cell.

35 The vaccine contains a housekeeping epitope in a concentration effective to cause a pAPC or populations of pAPCs to display housekeeping epitopes. Advantageously, the vaccine can

include a plurality of housekeeping epitopes or one or more housekeeping epitopes optionally in combination with one or more immune epitopes. Formulations of the vaccine contain peptides and/or nucleic acids in a concentration sufficient to cause pAPCs to present the epitopes. The formulations preferably contain epitopes in a total concentration of about 1 μ g-1mg/100 μ l of vaccine preparation. Conventional dosages and dosing for peptide vaccines and/or nucleic acid vaccines can be used with the present invention, and such dosing regimens are well understood in the art. In one embodiment, a single dosage for an adult human may advantageously be from about 1 to about 5000 μ l of such a composition, administered one time or multiple times, e.g., in 2, 3, 4 or more dosages separated by 1 week, 2 weeks, 1 month, or more. insulin pump delivers 1 ul per hour (lowest frequency) ref intranodal method patent.

The compositions and methods of the invention disclosed herein further contemplate incorporating adjuvants into the formulations in order to enhance the performance of the vaccines. Specifically, the addition of adjuvants to the formulations is designed to enhance the delivery or uptake of the epitopes by the pAPCs. The adjuvants contemplated by the present invention are known by those of skill in the art and include, for example, GMCSF, GCSF, IL-2, IL-12, BCG, tetanus toxoid, osteopontin, and ETA-1.

In some embodiments of the invention, the vaccines can include a recombinant organism, such as a virus, bacterium or parasite, genetically engineered to express an epitope in a host. For example, *Listeria monocytogenes*, a gram-positive, facultative intracellular bacterium, is a potent vector for targeting TuAAs to the immune system. In a preferred embodiment, this vector can be engineered to express a housekeeping epitope to induce therapeutic responses. The normal route of infection of this organism is through the gut and can be delivered orally. In another embodiment, an adenovirus (Ad) vector encoding a housekeeping epitope for a TuAA can be used to induce anti-virus or anti-tumor responses. Bone marrow-derived dendritic cells can be transduced with the virus construct and then injected, or the virus can be delivered directly via subcutaneous injection into an animal to induce potent T-cell responses. Another embodiment employs a recombinant vaccinia virus engineered to encode amino acid sequences corresponding to a housekeeping epitope for a TAA. Vaccinia viruses carrying constructs with the appropriate nucleotide substitutions in the form of a minigene construct can direct the expression of a housekeeping epitope, leading to a therapeutic T cell response against the epitope.

The immunization with DNA requires that APCs take up the DNA and express the encoded proteins or peptides. It is possible to encode a discrete class I peptide on the DNA. By immunizing with this construct, APCs can be caused to express a housekeeping epitope, which is then displayed on class I MHC on the surface of the cell for stimulating an appropriate CTL response. Constructs generally relying on termination of translation or non-proteasomal proteases for generation of proper termini of housekeeping epitopes have been described in PCT Publication

WO 01/82963 and U.S. Patent application No. 09/561,572 entitled EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS, filed on April 28, 2000. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

5 As mentioned, it can be desirable to express housekeeping peptides in the context of a larger protein. Processing can be detected even when a small number of amino acids are present beyond the terminus of an epitope. Small peptide hormones are usually proteolytically processed from longer translation products, often in the size range of approximately 60-120 amino acids. This fact has led some to assume that this is the minimum size that can be efficiently translated. In
10 some embodiments, the housekeeping peptide can be embedded in a translation product of at least about 60 amino acids. In other embodiments the housekeeping peptide can be embedded in a translation product of at least about 50, 30, or 15 amino acids.

Due to differential proteasomal processing, the immune proteasome of the pAPC produces peptides that are different from those produced by the housekeeping proteasome in peripheral body
15 cells. Thus, in expressing a housekeeping peptide in the context of a larger protein, it is preferably expressed in the APC in a context other than its full length native sequence, because, as a housekeeping epitope, it is generally only efficiently processed from the native protein by the housekeeping proteasome, which is not active in the APC. In order to encode the housekeeping epitope in a DNA sequence encoding a larger protein, it is useful to find flanking areas on either
20 side of the sequence encoding the epitope that permit appropriate cleavage by the immune proteasome in order to liberate that housekeeping epitope. Altering flanking amino acid residues at the N-terminus and C-terminus of the desired housekeeping epitope can facilitate appropriate cleavage and generation of the housekeeping epitope in the APC. Sequences embedding housekeeping epitopes can be designed *de novo* and screened to determine which can be
25 successfully processed by immune proteasomes to liberate housekeeping epitopes.

Alternatively, another strategy is very effective for identifying sequences allowing production of housekeeping epitopes in APC. A contiguous sequence of amino acids can be generated from head to tail arrangement of one or more housekeeping epitopes. A construct expressing this sequence is used to immunize an animal, and the resulting T cell response is
30 evaluated to determine its specificity to one or more of the epitopes in the array. By definition, these immune responses indicate housekeeping epitopes that are processed in the pAPC effectively. The necessary flanking areas around this epitope are thereby defined. The use of flanking regions of about 4-6 amino acids on either side of the desired peptide can provide the necessary information to facilitate proteasome processing of the housekeeping epitope by the immune
35 proteasome. Therefore, a sequence ensuring epitope synchronization of approximately 16-22 amino acids can be inserted into, or fused to, any protein sequence effectively to result in that

housekeeping epitope being produced in an APC. In alternate embodiments the whole head-to-tail array of epitopes, or just the epitopes immediately adjacent to the correctly processed housekeeping epitope can be similarly transferred from a test construct to a vaccine vector.

In a preferred embodiment, the housekeeping epitopes can be embedded between known
5 immune epitopes, or segments of such, thereby providing an appropriate context for processing. The abutment of housekeeping and immune epitopes can generate the necessary context to enable the immune proteasome to liberate the housekeeping epitope, or a larger fragment, preferably including a correct C-terminus. It can be useful to screen constructs to verify that the desired epitope is produced. The abutment of housekeeping epitopes can generate a site cleavable by the
10 immune proteasome. Some embodiments of the invention employ known epitopes to flank housekeeping epitopes in test substrates; in others, screening as described below are used whether the flanking regions are arbitrary sequences or mutants of the natural flanking sequence, and whether or not knowledge of proteasomal cleavage preferences are used in designing the substrates.

15 Cleavage at the mature N-terminus of the epitope, while advantageous, is not required, since a variety of N-terminal trimming activities exist in the cell that can generate the mature N-terminus of the epitope subsequent to proteasomal processing. It is preferred that such N-terminal extension be less than about 25 amino acids in length and it is further preferred that the extension have few or no proline residues. Preferably, in screening, consideration is given not only to
20 cleavage at the ends of the epitope (or at least at its C-terminus), but consideration also can be given to ensure limited cleavage within the epitope.

Shotgun approaches can be used in designing test substrates and can increase the efficiency of screening. In one embodiment multiple epitopes can be assembled one after the other, with individual epitopes possibly appearing more than once. The substrate can be screened to determine
25 which epitopes can be produced. In the case where a particular epitope is of concern a substrate can be designed in which it appears in multiple different contexts. When a single epitope appearing in more than one context is liberated from the substrate additional secondary test substrates, in which individual instances of the epitope are removed, disabled, or are unique, can be used to determine which are being liberated and truly constitute sequences ensuring epitope synchronization.

30 Several readily practicable screens exist. A preferred *in vitro* screen utilizes proteasomal digestion analysis, using purified immune proteasomes, to determine if the desired housekeeping epitope can be liberated from a synthetic peptide embodying the sequence in question. The position of the cleavages obtained can be determined by techniques such as mass spectrometry, HPLC, and N-terminal pool sequencing; as described in greater detail in U. S. Patent Applications entitled
35 METHOD OF EPITOPE DISCOVERY, EPITOPE SYNCHRONIZATION IN ANTIGEN

PRESENTING CELLS, PCT Publication, U.S. applications and Provisional U. S. Patent Applications entitled EPITOPE SEQUENCES.

Alternatively, *in vivo* screens such as immunization or target sensitization can be employed. For immunization a nucleic acid construct capable of expressing the sequence in question is used. Harvested CTL can be tested for their ability to recognize target cells presenting the housekeeping epitope in question. Such targets cells are most readily obtained by pulsing cells expressing the appropriate MHC molecule with synthetic peptide embodying the mature housekeeping epitope. Alternatively, cells known to express housekeeping proteasome and the antigen from which the housekeeping epitope is derived, either endogenously or through genetic engineering, can be used. To use target sensitization as a screen, CTL, or preferably a CTL clone, that recognizes the housekeeping epitope can be used. In this case it is the target cell that expresses the embedded housekeeping epitope (instead of the pAPC during immunization) and it must express immune proteasome. Generally, the target cell can be transformed with an appropriate nucleic acid construct to confer expression of the embedded housekeeping epitope. Loading with a synthetic peptide embodying the embedded epitope using peptide loaded liposomes or a protein transfer reagent such as BIOPORTER™ (Gene Therapy Systems, San Diego, CA) represents an alternative.

Additional guidance on nucleic acid constructs useful as vaccines in accordance with the present invention are disclosed in WO 01/82963 and U.S. Patent Application No. 09/561,572 entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS," filed on April 28, 2000. Further, expression vectors and methods for their design, which are useful in accordance with the present invention are disclosed in PCT Publication WO 03/063770; U.S. Patent Application No. 10/292,413, filed on November 7, 2002; and U.S. Provisional Application No. 60/336,968 (attorney docket number CTLIMM.022PR) entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN," filed on 11/7/2001. The teaching and embodiments disclosed in said PCT publications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

A preferred embodiment of the present invention includes a method of administering a vaccine including an epitope (or epitopes) to induce a therapeutic immune response. The vaccine is administered to a patient in a manner consistent with the standard vaccine delivery protocols that are known in the art. Methods of administering epitopes of TAAs including, without limitation, transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, and mucosal administration, including delivery by injection, instillation or inhalation. A particularly useful method of vaccine delivery to elicit a CTL response is disclosed in Australian Patent No. 739189 issued January 17, 2002; PCT Publication No. WO 099/02183; U.S. Patent

Application No. 09/380,534, filed on September 1, 1999; a Continuation-in-Part thereof U.S. Patent Application No. 09/776,232 both entitled "A METHOD OF INDUCING A CTL RESPONSE," filed on February 2, 2001, published as 20020007173; and PCT Publication No. WO 02/062368. The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

Reagents Recognizing Epitopes

In another aspect of the invention, proteins with binding specificity for the epitope and/or the epitope-MHC molecule complex are contemplated, as well as the isolated cells by which they can be expressed. In one set of embodiments these reagents take the form of immunoglobulins: polyclonal sera or monoclonal antibodies (mAb), methods for the generation of which are well known in the art. Generation of mAb with specificity for peptide-MHC molecule complexes is known in the art. See, for example, Aharoni et al. *Nature* 351:147-150, 1991; Andersen et al. *Proc. Natl. Acad. Sci. USA* 93:1820-1824, 1996; Dadaglio et al. *Immunity* 6:727-738, 1997; Duc et al. *Int. Immunol.* 5:427-431, 1993; Eastman et al. *Eur. J. Immunol.* 26:385-393, 1996; Engberg et al. *Immunotechnology* 4:273-278, 1999; Porgdor et al. *Immunity* 6:715-726, 1997; Puri et al. *J. Immunol.* 158:2471-2476, 1997; and Polakova, K., et al. *J. Immunol.* 165 342-348, 2000.

In other embodiments the compositions can be used to induce and generate, *in vivo* and *in vitro*, T-cells specific for the any of the epitopes and/or epitope-MHC complexes. In preferred embodiments the epitope can be any one or more of those listed in TABLE 1, for example. Thus, embodiments also relate to and include isolated T cells, T cell clones, T cell hybridomas, or a protein containing the T cell receptor (TCR) binding domain derived from the cloned gene, as well as a recombinant cell expressing such a protein. Such TCR derived proteins can be simply the extra-cellular domains of the TCR, or a fusion with portions of another protein to confer a desired property or function. One example of such a fusion is the attachment of TCR binding domains to the constant regions of an antibody molecule so as to create a divalent molecule. The construction and activity of molecules following this general pattern have been reported, for example, Plaksin, D. et al. *J. Immunol.* 158:2218-2227, 1997 and Lebowitz, M.S. et al. *Cell Immunol.* 192:175-184, 1999. The more general construction and use of such molecules is also treated in U.S. patent 5,830,755 entitled T CELL RECEPTORS AND THEIR USE IN THERAPEUTIC AND DIAGNOSTIC METHODS.

The generation of such T cells can be readily accomplished by standard immunization of laboratory animals, and reactivity to human target cells can be obtained by immunizing with human target cells or by immunizing HLA-transgenic animals with the antigen/epitope. For some therapeutic approaches T cells derived from the same species are desirable. While such a cell can be created by cloning, for example, a murine TCR into a human T cell as contemplated above, *in*

vitro immunization of human cells offers a potentially faster option. Techniques for *in vitro* immunization, even using naive donors, are known in the field, for example, Stauss et al., *Proc. Natl. Acad. Sci. USA* 89:7871-7875, 1992; Salgaller et al. *Cancer Res.* 55:4972-4979, 1995; Tsai et al., *J. Immunol.* 158:1796-1802, 1997; and Chung et al., *J. Immunother.* 22:279-287, 1999.

5 Any of these molecules can be conjugated to enzymes, radiochemicals, fluorescent tags, and toxins, so as to be used in the diagnosis (imaging or other detection), monitoring, and treatment of the pathogenic condition associated with the epitope. Thus a toxin conjugate can be administered to kill tumor cells, radiolabeling can facilitate imaging of epitope positive tumor, an enzyme conjugate can be used in an ELISA-like assay to diagnose cancer and confirm epitope
10 expression in biopsied tissue. In a further embodiment, such T cells as set forth above, following expansion accomplished through stimulation with the epitope and/or cytokines, can be administered to a patient as an adoptive immunotherapy.

Reagents Comprising Epitopes

A further aspect of the invention provides isolated epitope-MHC complexes. In a
15 particularly advantageous embodiment of this aspect of the invention, the complexes can be soluble, multimeric proteins such as those described in U. S. Patent No. 5,635,363 (tetramers) or U. S. Patent No. 6,015,884 (Ig-dimers). Such reagents are useful in detecting and monitoring specific T cell responses, and in purifying such T cells.

Isolated MHC molecules complexed with epitopic peptides can also be incorporated into
20 planar lipid bilayers or liposomes. Such compositions can be used to stimulate T cells *in vitro* or, in the case of liposomes, *in vivo*. Co-stimulatory molecules (e.g. B7, CD40, LFA-3) can be incorporated into the same compositions or, especially for *in vitro* work, co-stimulation can be provided by anti-co-receptor antibodies (e.g. anti-CD28, anti-CD154, anti-CD2) or cytokines (e.g. IL-2, IL-12). Such stimulation of T cells can constitute vaccination, drive expansion of T cells *in*
25 *vitro* for subsequent infusion in an immunotherapy, or constitute a step in an assay of T cell function.

The epitope, or more directly its complex with an MHC molecule, can be an important constituent of functional assays of antigen-specific T cells at either an activation or readout step or both. Of the many assays of T cell function current in the art (detailed procedures can be found in
30 standard immunological references such as *Current Protocols in Immunology* 1999 John Wiley & Sons Inc., N.Y.) two broad classes can be defined, those that measure the response of a pool of cells and those that measure the response of individual cells. Whereas the former conveys a global measure of the strength of a response, the latter allows determination of the relative frequency of responding cells. Examples of assays measuring global response are cytotoxicity assays, ELISA,
35 and proliferation assays detecting cytokine secretion. Assays measuring the responses of individual cells (or small clones derived from them) include limiting dilution analysis (LDA),

ELISPOT, flow cytometric detection of unsecreted cytokine (described in U.S. Patent No. 5,445,939, entitled "METHOD FOR ASSESSMENT OF THE MONONUCLEAR LEUKOCYTE IMMUNE SYSTEM" and U.S. Patent Nos 5,656,446; and 5,843,689, both entitled "METHOD FOR THE ASSESSMENT OF THE MONONUCLEAR LEUKOCYTE IMMUNE SYSTEM,"

5 reagents for which are sold by Becton, Dickinson & Company under the tradename 'FASTIMMUNE') and detection of specific TCR with tetramers or Ig-dimers as stated and referenced above. The comparative virtues of these techniques have been reviewed in Yee, C. et al. *Current Opinion in Immunology*, 13:141-146, 2001. Additionally detection of a specific TCR rearrangement or expression can be accomplished through a variety of established nucleic acid

10 based techniques, particularly in situ and single-cell PCR techniques, as will be apparent to one of skill in the art.

These functional assays are used to assess endogenous levels of immunity, response to an immunologic stimulus (e.g. a vaccine), and to monitor immune status through the course of a disease and treatment. Except when measuring endogenous levels of immunity, any of these assays

15 presume a preliminary step of immunization, whether *in vivo* or *in vitro* depending on the nature of the issue being addressed. Such immunization can be carried out with the various embodiments of the invention described above or with other forms of immunogen (e.g., pAPC-tumor cell fusions) that can provoke similar immunity. With the exception of PCR and tetramer/Ig-dimer type analyses which can detect expression of the cognate TCR, these assays generally benefit from a

20 step of *in vitro* antigenic stimulation which can advantageously use various embodiments of the invention as described above in order to detect the particular functional activity (highly cytolytic responses can sometimes be detected directly). Finally, detection of cytolytic activity requires epitope-displaying target cells, which can be generated using various embodiments of the invention. The particular embodiment chosen for any particular step depends on the question to be

25 addressed, ease of use, cost, and the like, but the advantages of one embodiment over another for any particular set of circumstances will be apparent to one of skill in the art.

The peptide MHC complexes described in this section have traditionally been understood to be non-covalent associations. However it is possible, and can be advantageous, to create a covalent linkages, for example by encoding the epitope and MHC heavy chain or the epitope, β 2-microglobulin, and MHC heavy chain as a single protein (Yu, Y.L.Y., et al., *J. Immunol.* 168:3145-3149, 2002; Mottez, E., et al., *J. Exp. Med.* 181:493,1995; Dela Cruz, C. S., et al., *Int. Immunol.* 12:1293, 2000; Mage, M. G., et al., *Proc. Natl. Acad. Sci. USA* 89:10658,1992; Toshitani, K., et al., *Proc. Natl. Acad. Sci. USA* 93:236,1996; Lee, L., et al., *Eur. J. Immunol.* 24:2633,1994; Chung, D. H., et al., *J. Immunol.* 163:3699,1999; Uger, R. A. and B. H. Barber, *J. Immunol.* 160:1598,

30 1998; Uger, R. A., et al., *J. Immunol.* 162:6024,1999; and White, J., et al., *J. Immunol.* 162:2671, 1999). Such constructs can have superior stability and overcome roadblocks in the processing-

presentation pathway. They can be used in the already described vaccines, reagents, and assays in similar fashion.

Tumor Associated Antigens

Epitopes of the present invention are derived from the TuAAs tyrosinase (SEQ ID NO. 2),
5 SSX-2, (SEQ ID NO. 3), PSMA (prostate-specific membrane antigen) (SEQ ID NO. 4), MAGE-1
(SEQ ID NO. 71), MAGE-2 (SEQ ID NO. 72), MAGE-3 (SEQ ID NO. 73), PRAME, (SEQ ID NO.
77), PSA, (SEQ ID NO. 78), PSCA, (SEQ ID NO. 79), CEA (carcinoembryonic antigen), (SEQ ID
NO. 88), SCP-1 (SEQ ID NO. 92), GAGE-1, (SEQ ID NO. 96), survivin, (SEQ ID NO. 98), Melan-
A/MART-1 (SEQ ID NO. 100), and BAGE (SEQ ID NO. 102). The natural coding sequences for
10 these fifteen proteins, or any segments within them, can be determined from their cDNA or
complete coding (cds) sequences, SEQ ID NOS. 5-7, 81-83, 85-87, 89, 93, 97, 99, 101, and 103,
respectively.

Tyrosinase is a melanin biosynthetic enzyme that is considered one of the most specific
markers of melanocytic differentiation. Tyrosinase is expressed in few cell types, primarily in
15 melanocytes, and high levels are often found in melanomas. The usefulness of tyrosinase as a
TuAA is taught in U.S. Patent 5,747,271 entitled "METHOD FOR IDENTIFYING INDIVIDUALS
SUFFERING FROM A CELLULAR ABNORMALITY SOME OF WHOSE ABNORMAL
CELLS PRESENT COMPLEXES OF HLA-A2/TYROSINASE DERIVED PEPTIDES, AND
METHODS FOR TREATING SAID INDIVIDUALS."

20 GP100, also known as PMel17, also is a melanin biosynthetic protein expressed at high
levels in melanomas. GP100 as a TuAA is disclosed in U.S. Patent 5,844,075 entitled
"MELANOMA ANTIGENS AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
METHODS."

Melan-A, also called MART-1 (Melanoma Antigen Recognized by T cells), is another
25 melanin biosynthetic protein expressed at high levels in melanomas. The usefulness of Melan-
A/MART-1 as a TuAA is taught in U.S. Patent Nos. 5,874,560 and 5,994,523 both entitled
"MELANOMA ANTIGENS AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
METHODS," as well as U.S. Patent No. 5,620,886, entitled "ISOLATED NUCLEIC ACID
SEQUENCE CODING FOR A TUMOR REJECTION ANTIGEN PRECURSOR PROCESSED
30 TO AT LEAST ONE TUMOR REJECTION ANTIGEN PRESENTED BY HLA-A2."

SSX-2, also know as Hom-Mel-40, is a member of a family of highly conserved cancer-
testis antigens (Gure, A.O. et al. *Int. J. Cancer* 72:965-971, 1997). Its identification as a TuAA is
taught in U.S. Patent 6,025,191 entitled "ISOLATED NUCLEIC ACID MOLECULES WHICH
35 ENCODE A MELANOMA SPECIFIC ANTIGEN AND USES THEREOF." Cancer-testis
antigens are found in a variety of tumors, but are generally absent from normal adult tissues except
testis. Expression of different members of the SSX family have been found variously in tumor cell

lines. Due to the high degree of sequence identity among SSX family members, similar epitopes from more than one member of the family will be generated and able to bind to an MHC molecule, so that some vaccines directed against one member of this family can cross-react and be effective against other members of this family (see example 3 below).

5 MAGE-1, MAGE-2, and MAGE-3 are members of another family of cancer-testis antigens originally discovered in melanoma (MAGE is a contraction of melanoma-associated antigen) but found in a variety of tumors. The identification of MAGE proteins as TuAAs is taught in U.S. Patent 5,342,774 entitled NUCLEOTIDE SEQUENCE ENCODING THE TUMOR REJECTION ANTIGEN PRECURSOR, MAGE-1, and in numerous subsequent patents. Currently there are 17
10 entries for (human) MAGE in the SWISS Protein database. There is extensive similarity among these proteins so in many cases, an epitope from one can induce a cross-reactive response to other members of the family. A few of these have not been observed in tumors, most notably MAGE-H1 and MAGE-D1, which are expressed in testes and brain, and bone marrow stromal cells, respectively. The possibility of cross-reactivity on normal tissue is ameliorated by the fact that they
15 are among the least similar to the other MAGE proteins.

 GAGE-1 is a member of the GAGE family of cancer testis antigens (Van den Eynde, B., et al., *J. Exp. Med.* 182: 689-698, 1995; U.S. Patent Nos. 5,610,013; 5,648,226; 5,858,689; 6,013,481; and 6,069,001). The PubGene database currently lists 12 distinct accessible members, some of which are synonymously known as PAGE or XAGE. GAGE-1 through GAGE-8 have a very high
20 degree of sequence identity, so most epitopes can be shared among multiple members of the family.

 BAGE is a cancer-testis antigen commonly expressed in melanoma, particularly metastatic melanoma, as well as in carcinomas of the lung, breast, bladder, and squamous cells of the head and neck. Its usefulness as a TuAA is taught in U.S. Patent Nos. 5,683,88 entitled "TUMOR REJECTION ANTIGENS WHICH CORRESPOND TO AMINO ACID SEQUENCES IN TUMOR
25 REJECTION ANTIGEN PRECURSOR BAGE, AND USES THEREOF" and 5,571,711 entitled "ISOLATED NUCLEIC ACID MOLECULES CODING FOR BAGE TUMOR REJECTION ANTIGEN PRECURSORS."

 NY-ESO-1, is a cancer-testis antigen found in a wide variety of tumors, also known as CTAG-1 (Cancer-Testis Antigen-1) and CAG-3 (Cancer Antigen-3). NY-ESO-1 as a TuAA is
30 disclosed in U.S. Patent 5,804,381 entitled ISOLATED NUCLEIC ACID MOLECULE ENCODING AN ESOPHAGEAL CANCER ASSOCIATED ANTIGEN, THE ANTIGEN ITSELF, AND USES THEREOF. A paralogous locus encoding antigens with extensive sequence identity, LAGE-1a/s (SEQ ID NO. 75) and LAGE-1b/L (SEQ ID NO. 76), have been disclosed in publicly available assemblies of the human genome, and have been concluded to arise through alternate
35 splicing. Additionally, CT-2 (or CTAG-2, Cancer-Testis Antigen-2) appears to be either an allele, a mutant, or a sequencing discrepancy of LAGE-1b/L. Due to the extensive sequence identity,

many epitopes from NY-ESO-1 can also induce immunity to tumors expressing these other antigens. See figure 1. The proteins are virtually identical through amino acid 70. From 71-134 the longest run of identities between NY-ESO-1 and LAGE is 6 residues, but potentially cross-reactive sequences are present. And from 135-180 NY-ESO and LAGE-1a/s are identical except for a single residue, but LAGE-1b/L is unrelated due to the alternate splice. The CAMEL and LAGE-2 antigens appear to derive from the LAGE-1 mRNA, but from alternate reading frames, thus giving rise to unrelated protein sequences. More recently, GenBank Accession AF277315.5, Homo sapiens chromosome X clone RP5-865E18, RP5-1087L19, complete sequence, reports three independent loci in this region which are labeled as LAGE1 (corresponding to CTAG-2 in the genome assemblies), plus LAGE2-A and LAGE2-B (both corresponding to CTAG-1 in the genome assemblies).

PSMA (prostate-specific membranes antigen), a TuAA described in U.S. Patent 5,538,866 entitled "PROSTATE-SPECIFIC MEMBRANES ANTIGEN", is expressed by normal prostate epithelium and, at a higher level, in prostatic cancer. It has also been found in the neovasculature of non-prostatic tumors. PSMA can thus form the basis for vaccines directed to both prostate cancer and to the neovasculature of other tumors. This later concept is more fully described in U.S. Patent Publication No. 20030046714; PCT Publication No. WO 02/069907; and a provisional U.S. Patent application No. 60/274,063 entitled ANTI-NEOVASCULAR VACCINES FOR CANCER, filed March 7, 2001, and U.S. Application No. 10/094,699, attorney docket number CTLIMM.015A, filed on March 7, 2002, entitled "ANTI-NEOVASCULAR PREPARATIONS FOR CANCER." The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. Briefly, as tumors grow they recruit ingrowth of new blood vessels. This is understood to be necessary to sustain growth as the centers of unvascularized tumors are generally necrotic and angiogenesis inhibitors have been reported to cause tumor regression. Such new blood vessels, or neovasculature, express antigens not found in established vessels, and thus can be specifically targeted. By inducing CTL against neovascular antigens the vessels can be disrupted, interrupting the flow of nutrients to (and removal of wastes from) tumors, leading to regression.

Alternate splicing of the PSMA mRNA also leads to a protein with an apparent start at Met₅₈, thereby deleting the putative membrane anchor region of PSMA as described in U.S. Patent 5,935,818 entitled "ISOLATED NUCLEIC ACID MOLECULE ENCODING ALTERNATIVELY SPLICED PROSTATE-SPECIFIC MEMBRANES ANTIGEN AND USES THEREOF." A protein termed PSMA-like protein, Genbank accession number AF261715, is nearly identical to amino acids 309-750 of PSMA and has a different expression profile. Thus the most preferred epitopes are those with an N-terminus located from amino acid 58 to 308.

PRAME, also known as MAPE, DAGE, and OIP4, was originally observed as a melanoma antigen. Subsequently, it has been recognized as a CT antigen, but unlike many CT antigens (e.g., MAGE, GAGE, and BAGE) it is expressed in acute myeloid leukemias. PRAME is a member of the MAPE family which consists largely of hypothetical proteins with which it shares limited sequence similarity. The usefulness of PRAME as a TuAA is taught in U.S. Patent 5,830,753
5 entitled "ISOLATED NUCLEIC ACID MOLECULES CODING FOR TUMOR REJECTION ANTIGEN PRECURSOR DAGE AND USES THEREOF."

PSA, prostate specific antigen, is a peptidase of the kallikrein family and a differentiation antigen of the prostate. Expression in breast tissue has also been reported. Alternate names include
10 gamma-seminoprotein, kallikrein 3, seminogelase, seminin, and P-30 antigen. PSA has a high degree of sequence identity with the various alternate splicing products prostatic/glandular kallikrein-1 and -2, as well as kallikrein 4, which is also expressed in prostate and breast tissue. Other kallikreins generally share less sequence identity and have different expression profiles. Nonetheless, cross-reactivity that might be provoked by any particular epitope, along with the
15 likelihood that that epitope would be liberated by processing in non-target tissues (most generally by the housekeeping proteasome), should be considered in designing a vaccine.

PSCA, prostate stem cell antigen, and also known as SCAH-2, is a differentiation antigen preferentially expressed in prostate epithelial cells, and overexpressed in prostate cancers. Lower level expression is seen in some normal tissues including neuroendocrine cells of the digestive tract and collecting ducts of the kidney. PSCA is described in U.S. Patent 5,856,136 entitled "HUMAN
20 STEM CELL ANTIGENS."

Synaptonemal complex protein 1 (SCP-1), also known as HOM-TES-14, is a meiosis-associated protein and also a cancer-testis antigen (Tureci, O., et al. *Proc. Natl. Acad. Sci. USA* 95:5211-5216, 1998). As a cancer antigen its expression is not cell-cycle regulated and it is found
25 frequently in gliomas, breast, renal cell, and ovarian carcinomas. It has some similarity to myosins, but with few enough identities that cross-reactive epitopes are not an immediate prospect.

The ED-B domain of fibronectin is also a potential target. Fibronectin is subject to developmentally regulated alternative splicing, with the ED-B domain being encoded by a single exon that is used primarily in oncofetal tissues (Matsuura, H. and S. Hakomori *Proc. Natl. Acad. Sci. USA* 82:6517-6521, 1985; Camemolla, B. et al. *J. Cell Biol.* 108:1139-1148, 1989; Loidon-
30 Rosa, B. et al. *Cancer Res.* 50:1608-1612, 1990; Nicolo, G. et al. *Cell Differ. Dev.* 32:401-408, 1990; Borsi, L. et al. *Exp. Cell Res.* 199:98-105, 1992; Oyama, F. et al. *Cancer Res.* 53:2005-2011, 1993; Mandel, U. et al. *APMIS* 102:695-702, 1994; Farnoud, M.R. et al. *Int. J. Cancer* 61:27-34, 1995; Pujuguet, P. et al. *Am. J. Pathol.* 148:579-592, 1996; Gabler, U. et al. *Heart* 75:358-362, 1996; Chevalier, X. *Br. J. Rheumatol.* 35:407-415, 1996; Midulla, M. *Cancer Res.* 60:164-169, 2000).
35

The ED-B domain is also expressed in fibronectin of the neovasculature (Kaczmarek, J. et al. *Int. J. Cancer* 59:11-16, 1994; Castellani, P. et al. *Int. J. Cancer* 59:612-618, 1994; Neri, D. et al. *Nat. Biotech.* 15:1271-1275, 1997; Karelina, T.V. and A.Z. Eisen *Cancer Detect. Prev.* 22:438-444, 1998; Tarli, L. et al. *Blood* 94:192-198, 1999; Castellani, P. et al. *Acta Neurochir. (Wien)* 142:277-282, 2000). As an oncofetal domain, the ED-B domain is commonly found in the fibronectin expressed by neoplastic cells in addition to being expressed by the neovasculature. Thus, CTL-inducing vaccines targeting the ED-B domain can exhibit two mechanisms of action: direct lysis of tumor cells, and disruption of the tumor's blood supply through destruction of the tumor-associated neovasculature. As CTL activity can decay rapidly after withdrawal of vaccine, interference with normal angiogenesis can be minimal. The design and testing of vaccines targeted to neovasculature is described in Provisional U.S. Patent Application No. 60/274,063 entitled "ANTI-NEOVASCULATURE VACCINES FOR CANCER" and in U.S. Patent Application No. 10/094,699, attorney docket number CTLIMM.015A, entitled "ANTI-NEOVASCULATURE PREPARATIONS FOR CANCER, filed on date even with this application (March 7, 2002). A tumor cell line is disclosed in Provisional U.S. Application No. 60/363,131, filed on March 7, 2002, attorney docket number CTLIMM.028PR, entitled "HLA-TRANSGENIC MURINE TUMOR CELL LINE."

Carcinoembryonic antigen (CEA) is a paradigmatic oncofetal protein first described in 1965 (Gold and Freedman, *J. Exp. Med.* 121: 439-462, 1965. Fuller references can be found in the Online Medelian Inheritance in Man; record *114890). It has officially been renamed carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). Its expression is most strongly associated with adenocarcinomas of the epithelial lining of the digestive tract and in fetal colon. CEA is a member of the immunoglobulin supergene family and the defining member of the CEA subfamily.

Survivin, also known as Baculoviral IAP Repeat-Containing Protein 5 (BIRC5), is another protein with an oncofetal pattern of expression. It is a member of the inhibitor of apoptosis protein (IAP) gene family. It is widely overexpressed in cancers (Ambrosini, G. et al., *Nat. Med.* 3:917-921, 1997; Velculescu V.E. et al., *Nat. Genet.* 23:387-388, 1999) and its function as an inhibitor of apoptosis is believed to contribute to the malignant phenotype.

HER2/NEU is an oncogene related to the epidermal growth factor receptor (van de Vijver, et al., *New Eng. J. Med.* 319:1239-1245, 1988), and apparently identical to the c-ERBB2 oncogene (Di Fiore, et al., *Science* 237: 178-182, 1987). The over-expression of ERBB2 has been implicated in the neoplastic transformation of prostate cancer. As HER2 it is amplified and over-expressed in 25-30% of breast cancers among other tumors where expression level is correlated with the aggressiveness of the tumor (Slamon, et al., *New Eng. J. Med.* 344:783-792, 2001). A more detailed description is available in the Online Medelian Inheritance in Man; record *164870.

Useful epitopes were identified and tested as described in the following examples. However, these examples are intended for illustration purposes only, and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

5 Example 1

Manufacture of epitopes.

A. Synthetic production of epitopes

Peptides having an amino acid sequence of any of SEQ ID NO: 1, 8, 9, 11-23, 26-29, 32-44, 47-54, 56-63, 66-68, or 108-602 are synthesized using either FMOC or tBOC solid phase synthesis methodologies. After synthesis, the peptides are cleaved from their supports with either trifluoroacetic acid or hydrogen fluoride, respectively, in the presence of appropriate protective scavengers. After removing the acid by evaporation, the peptides are extracted with ether to remove the scavengers and the crude, precipitated peptide is then lyophilized. Purity of the crude peptides is determined by HPLC, sequence analysis, amino acid analysis, counterion content analysis and other suitable means. If the crude peptides are pure enough (greater than or equal to about 90% pure), they can be used as is. If purification is required to meet drug substance specifications, the peptides are purified using one or a combination of the following: re-precipitation; reverse-phase, ion exchange, size exclusion or hydrophobic interaction chromatography; or counter-current distribution.

20 Drug product formulation

GMP-grade peptides are formulated in a parenterally acceptable aqueous, organic, or aqueous-organic buffer or solvent system in which they remain both physically and chemically stable and biologically potent. Generally, buffers or combinations of buffers or combinations of buffers and organic solvents are appropriate. The pH range is typically between 6 and 9. Organic modifiers or other excipients can be added to help solubilize and stabilize the peptides. These include detergents, lipids, co-solvents, antioxidants, chelators and reducing agents. In the case of a lyophilized product, sucrose or mannitol or other lyophilization aids can be added. Peptide solutions are sterilized by membrane filtration into their final container-closure system and either lyophilized for dissolution in the clinic, or stored until use.

30 B. Construction of expression vectors for use as nucleic acid vaccines

The construction of three generic epitope expression vectors is presented below. The particular advantages of these designs are set forth in PCT Publication No. WO 01/82963 and U.S. Patent Application No. 09/561,572 entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS." Additional vectors strategies for their design are disclosed in PCT Publication WO 03/063770; U.S. Patent Application No. 10/292,413, filed on November 7, 2002; and Provisional U.S. Patent application No. 60/336,968 entitled

"EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN," filed on November 7, 2001. The teachings and embodiments disclosed in said PCT publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

5 A suitable *E. coli* strain was then transfected with the plasmid and plated out onto a selective medium. Several colonies were grown up in suspension culture and positive clones were identified by restriction mapping. The positive clone was then grown up and aliquotted into storage vials and stored at -70°C.

10 A mini-prep (QIAprep Spin Mini-prep: Qiagen, Valencia, CA) of the plasmid was then made from a sample of these cells and automated fluorescent dideoxy sequence analysis was used to confirm that the construct had the desired sequence.

B.1 Construction of pVAX-EP1-IRES-EP2

Overview:

15 The starting plasmid for this construct is pVAX1 purchased from Invitrogen (Carlsbad, CA). Epitopes EP1 and EP2 were synthesized by GIBCO BRL (Rockville, MD). The IRES was excised from pIRES purchased from Clontech (Palo Alto, CA).

Procedure:

- 20 1. pIRES was digested with EcoRI and NotI. The digested fragments were separated by agarose gel electrophoresis, and the IRES fragment was purified from the excised band.
2. pVAX1 was digested with EcoRI and NotI, and the pVAX1 fragment was gel-purified.
3. The purified pVAX1 and IRES fragments were then ligated together.
4. Competent *E. coli* of strain DH5 α were transformed with the ligation mixture.
5. Minipreps were made from 4 of the resultant colonies.
- 25 6. Restriction enzyme digestion analysis was performed on the miniprep DNA. One recombinant colony having the IRES insert was used for further insertion of EP1 and EP2. This intermediate construct was called pVAX-IRES.
7. Oligonucleotides encoding EP1 and EP2 were synthesized.
8. EP1 was subcloned into pVAX-IRES between AflII and EcoRI sites, to make pVAX-EP1-IRES;
- 30 9. EP2 was subcloned into pVAX-EP1-IRES between SalI and NotI sites, to make the final construct pVAX-EP1-IRES-EP2.
10. The sequence of the EP1-IRES-EP2 insert was confirmed by DNA sequencing.

B 2. Construction of pVAX-EP1-IRES-EP2-ISS-NIS

Overview:

The starting plasmid for this construct was pVAX-EP1-IRES-EP2 (Example 1). The ISS (immunostimulatory sequence) introduced into this construct is AACGTT, and the NIS (standing
5 for nuclear import sequence) used is the SV40 72bp repeat sequence. ISS-NIS was synthesized by GIBCO BRL. See Figure 2.

Procedure:

1. pVAX-EP1-IRES-EP2 was digested with NruI; the linearized plasmid was gel-purified.
2. ISS-NIS oligonucleotide was synthesized.
- 10 3. The purified linearized pVAX-EP1-IRES-EP2 and synthesized ISS-NIS were ligated together.
4. Competent E. coli of strain DH5 α were transformed with the ligation product.
5. Minipreps were made from resultant colonies.
6. Restriction enzyme digestions of the minipreps were carried out.
- 15 7. The plasmid with the insert was sequenced.

B3. Construction of pVAX-EP2-UB-EP1

Overview:

The starting plasmid for this construct was pVAX1 (Invitrogen). EP2 and EP1 were synthesized by GIBCO BRL. Wild type Ubiquitin cDNA encoding the 76 amino acids in the
20 construct was cloned from yeast.

Procedure:

1. RT-PCR was performed using yeast mRNA. Primers were designed to amplify the complete coding sequence of yeast Ubiquitin.
2. The RT-PCR products were analyzed using agarose gel electrophoresis. A band with
25 the predicted size was gel-purified.
3. The purified DNA band was subcloned into pZERO1 at EcoRV site. The resulting clone was named pZERO-UB.
4. Several clones of pZERO-UB were sequenced to confirm the Ubiquitin sequence before further manipulations.
- 30 5. EP1 and EP2 were synthesized.
6. EP2, Ubiquitin and EP1 were ligated and the insert cloned into pVAX1 between BamHI and EcoRI, putting it under control of the CMV promoter.
7. The sequence of the insert EP2-UB-EP1 was confirmed by DNA sequencing.

Example 2Identification of useful epitope variants.

The 10-mer FLPWHRLFLL (SEQ ID NO. 1) is identified as a useful epitope. Based on this sequence, numerous variants are made. Variants exhibiting activity in HLA binding assays (see Example 3, section 6) are identified as useful, and are subsequently incorporated into vaccines. Variants that increase the stability of binding, assayed can be particularly useful, for example as described in WO 97/41440 entitled "Methods for Selecting and Producing T Cell Peptide Epitopes and Vaccines Incorporating Said Selected Epitopes." The teachings and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

The HLA-A2 binding of length variants of FLPWHRLFLL have been evaluated. Proteasomal digestion analysis indicates that the C-terminus of the 9-mer FLPWHRLFL (SEQ ID NO. 8) is also produced. Additionally the 9-mer LPWHRLFLL (SEQ ID NO. 9) can result from N-terminal trimming of the 10-mer. Both are predicted to bind to the HLA-A*0201 molecule, however of these two 9-mers, FLPWHRLFL displayed more significant binding and is preferred (see Figs. 3A and B).

In vitro proteasome digestion and N-terminal pool sequencing indicates that tyrosinase₂₀₇₋₂₁₆ (SEQ ID NO. 1) is produced more commonly than tyrosinase₂₀₇₋₂₁₅ (SEQ ID NO. 8), however the latter peptide displays superior immunogenicity, a potential concern in arriving at an optimal vaccine design. FLPWHRLFL, tyrosinase₂₀₇₋₂₁₅ (SEQ ID NO. 8) was used in an in vitro immunization of HLA-A2⁺ blood to generate CTL (see CTL Induction Cultures below). Using peptide pulsed T2 cells as targets in a standard chromium release assay it was found that the CTL induced by tyrosinase₂₀₇₋₂₁₅ (SEQ ID NO. 8) recognize tyrosinase₂₀₇₋₂₁₆ (SEQ ID NO. 1) targets equally well (see fig. 3C). These CTL also recognize the HLA-A2⁺, tyrosinase⁺ tumor cell lines 624.38 and HTB64, but not 624.28 an HLA-A2⁻ derivative of 624.38 (fig. 3C). Thus the relative amounts of these two epitopes produced in vivo, does not become a concern in vaccine design.

CTL induction cultures

PBMCs from normal donors were purified by centrifugation in Ficoll-Hypaque from buffy coats. All cultures were carried out using the autologous plasma (AP) to avoid exposure to potential xenogeneic pathogens and recognition of FBS peptides. To favor the in vitro generation of peptide-specific CTL, we employed autologous dendritic cells (DC) as APCs. DC were generated and CTL were induced with DC and peptide from PBMCs as described (Keogh et al., 2001). Briefly, monocyte-enriched cell fractions were cultured for 5 days with GM-CSF and IL-4 and were cultured for 2 additional days in culture media with 2 µg/ml CD40 ligand to induce maturation. 2 x10⁶ CD8⁺-enriched T lymphocytes/well and 2 x10⁵ peptide-pulsed DC/well were co-cultured in 24-well plates in 2 ml RPMI supplemented with 10% AP, 10 ng/ml IL-7 and 20

IU/ml IL-2. Cultures were restimulated on days 7 and 14 with autologous irradiated peptide-pulsed DC.

Sequence variants of FLPWHRLFL are constructed as follow. Consistent with the binding coefficient table (see Table 3) from the NIH/BIMAS MHC binding prediction program (see reference in example 3 below), binding can be improved by changing the L at position 9, an anchor position, to V. Binding can also be altered, though generally to a lesser extent, by changes at non-anchor positions. Referring generally to Table 3, binding can be increased by employing residues with relatively larger coefficients. Changes in sequence can also alter immunogenicity independently of their effect on binding to MHC. Thus binding and/or immunogenicity can be improved as follows:

By substituting F,L,M,W, or Y for P at position 3; these are all bulkier residues that can also improve immunogenicity independent of the effect on binding. The amine and hydroxyl-bearing residues, Q and N; and S and T; respectively, can also provoke a stronger, cross-reactive response.

By substituting D or E for W at position 4 to improve binding; this addition of a negative charge can also make the epitope more immunogenic, while in some cases reducing cross-reactivity with the natural epitope. Alternatively the conservative substitutions of F or Y can provoke a cross-reactive response.

By substituting F for H at position 5 to improve binding. H can be viewed as partially charged, thus in some cases the loss of charge can hinder cross-reactivity. Substitution of the fully charged residues R or K at this position can enhance immunogenicity without disrupting charge-dependent cross-reactivity.

By substituting I, L, M, V, F, W, or Y for R at position 6. The same caveats and alternatives apply here as at position 5.

By substituting W or F for L at position 7 to improve binding. Substitution of V, I, S, T, Q, or N at this position are not generally predicted to reduce binding affinity by this model (the NIH algorithm), yet can be advantageous as discussed above.

Y and W, which are equally preferred as the Fs at positions 1 and 8, can provoke a useful cross-reactivity. Finally, while substitutions in the direction of bulkiness are generally favored to improve immunogenicity, the substitution of smaller residues such as A, S, and C, at positions 3-7 can be useful according to the theory that contrast in size, rather than bulkiness per se, is an important factor in immunogenicity. The reactivity of the thiol group in C can introduce other properties as discussed in Chen, J.-L., et al. *J. Immunol.* 165:948-955, 2000.

Table 3. 9-mer Coefficient Table for HLA-A*0201*

HLA Coefficient table for file "A_0201_standard"									
Amino Acid Type	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th
A	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
C	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	1.000
D	0.075	0.100	0.400	4.100	1.000	1.000	0.490	1.000	0.003
E	0.075	1.400	0.064	4.100	1.000	1.000	0.490	1.000	0.003
F	4.600	0.050	3.700	1.000	3.800	1.900	5.800	5.500	0.015
G	1.000	0.470	1.000	1.000	1.000	1.000	0.130	1.000	0.015
H	0.034	0.050	1.000	1.000	1.000	1.000	1.000	1.000	0.015
I	1.700	9.900	1.000	1.000	1.000	2.300	1.000	0.410	2.100
K	3.500	0.100	0.035	1.000	1.000	1.000	1.000	1.000	0.003
L	1.700	72.000	3.700	1.000	1.000	2.300	1.000	1.000	4.300
M	1.700	52.000	3.700	1.000	1.000	2.300	1.000	1.000	1.000
N	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.015
P	0.022	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.003
Q	1.000	7.300	1.000	1.000	1.000	1.000	1.000	1.000	0.003
R	1.000	0.010	0.076	1.000	1.000	1.000	0.200	1.000	0.003
S	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.015
T	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.500
V	1.700	6.300	1.000	1.000	1.000	2.300	1.000	0.410	14.000
W	4.600	0.010	8.300	1.000	1.000	1.700	7.500	5.500	0.015
Y	4.600	0.010	3.200	1.000	1.000	1.500	1.000	5.500	0.015

*This table and other comparable data that are publicly available are useful in designing epitope variants and in determining whether a particular variant is substantially similar, or is functionally similar.

Example 3

Cluster Analysis (SSX-2₃₁₋₆₈).

1. Epitope cluster region prediction:

The computer algorithms: SYFPEITHI (internet [http:// syfpeithi.bmi-heidelberg.com/Scripts/MHCServer.dll/EpPredict.htm](http://syfpeithi.bmi-heidelberg.com/Scripts/MHCServer.dll/EpPredict.htm)), based on the book "MHC Ligands and Peptide Motifs" by H.G.Rammensee, J.Bachmann and S.Stevanovic; and HLA Peptide Binding Predictions (NIH) (internet [http:// access at bimas.dcrt.nih.gov/molbio/hla_bin](http://bimas.dcrt.nih.gov/molbio/hla_bin)), described in Parker, K. C., et al., *J. Immunol.* 152:163, 1994; were used to analyze the protein sequence of SSX-2 (GI:10337583). Epitope clusters (regions with higher than average density of peptide fragments with high predicted MHC affinity) were defined as described fully in U.S. Patent Application No. 09/561,571 entitled "EPITOPE CLUSTERS," filed on April 28, 2000. Using a epitope density ratio cutoff of 2, five and two clusters were defined using the SYFPETHI and NIH algorithms, respectively, and peptides score cutoffs of 16 (SYFPETHI) and 5 (NIH). The highest scoring peptide with the NIH algorithm, SSX-2₄₁₋₄₉, with an estimated halftime of dissociation of

>1000 min., does not overlap any other predicted epitope but does cluster with SSX-2₅₇₋₆₅ in the NIH analysis.

2. Peptide synthesis and characterization:

SSX-2₃₁₋₆₈, YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGFKATLP (SEQ ID NO. 10) was synthesized by MPS (Multiple Peptide Systems, San Diego, CA 92121) using standard solid phase chemistry. According to the provided 'Certificate of Analysis', the purity of this peptide was 95%.

3. Proteasome digestion:

Proteasome was isolated from human red blood cells using the proteasome isolation protocol described in PCT Publication No. WO 01/82963 and U.S. Patent Application No. 09/561,074 entitled "METHOD OF EPITOPE DISCOVERY," filed on April 28, 2000. The teachings and embodiments disclosed in said PCT publication and application are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. SDS-PAGE, western-blotting, and ELISA were used as quality control assays. The final concentration of proteasome was 4 mg/ml, which was determined by non-interfering protein assay (Geno Technologies Inc.). Proteasomes were stored at -70°C in 25 µl aliquots.

SSX-2₃₁₋₆₈ was dissolved in Milli-Q water, and a 2 mM stock solution prepared and 20µL aliquots stored at -20°C.

1 tube of proteasome (25 µL) was removed from storage at -70°C and thawed on ice. It was then mixed thoroughly with 12.5µL of 2mM peptide by repipetting (samples were kept on ice). A 5µL sample was immediately removed after mixing and transferred to a tube containing 1.25µL 10%TFA (final concentration of TFA was 2%); the T=0 min sample. The proteasome digestion reaction was then started and carried out at 37°C in a programmable thermal controller. Additional 5µL samples were taken out at 15, 30, 60, 120, 180 and 240 min respectively, the reaction was stopped by adding the sample to 1.25µL 10% TFA as before. Samples were kept on ice or frozen until being analyzed by MALDI-MS. All samples were saved and stored at -20°C for HPLC analysis and N-terminal sequencing. Peptide alone (without proteasome) was used as a blank control: 2 µL peptide + 4µL Tris buffer (20 mM, pH 7.6) + 1.5µL TFA.

4. MALDI-TOF MS measurements:

For each time point 0.3 µL of matrix solution (10mg/ml α-cyano-4-hydroxycinnamic acid in AcCN/H₂O (70:30)) was first applied on a sample slide, and then an equal volume of digested sample was mixed gently with matrix solution on the slide. The slide was allowed to dry at ambient air for 3-5 min. before acquiring the mass spectra. MS was performed on a Lasermat 2000 MALDI-TOF mass spectrometer that was calibrated with peptide/protein standards. To improve the accuracy of measurement, the molecular ion weight (MH⁺) of the peptide substrate was used as

an internal calibration standard. The mass spectrum of the T=120 min. digested sample is shown in figure 4.

5. MS data analysis and epitope identification:

To assign the measured mass peaks, the computer program MS-Product, a tool from the UCSF Mass Spectrometry Facility (<http://prospector.ucsf.edu/ucsfhtml3.4/msprod.htm>), was used to generate all possible fragments (N- and C-terminal ions, and internal fragments) and their corresponding molecular weights. Due to the sensitivity of the mass spectrometer, average molecular weight was used. The mass peaks observed over the course of the digestion were identified as summarized in Table 4.

10 Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1 binding sequences, the actual products of digestion can be checked after the fact for actual or
15 predicted binding to other MHC molecules. Selected results are shown in Table 5.

Table 4. SSX-2₃₁₋₆₈ Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH ⁺)
988.23	31-37	YFSKEEW	989.08
1377.68±2.38	31-40	YFSKEEWEKM	1377.68
1662.45±1.30	31-43	YFSKEEWEKMKAS	1663.90
2181.72±0.85	31-47	YFSKEEWEKMKASEKIF	2181.52
2346.6	31-48	YFSKEEWEKMKASEKIFY	2344.71
1472.16±1.54	38-49	EKMKASEKIFYV	1473.77
2445.78±1.18	31-49*	YFSKEEWEKMKASEKIFYV	2443.84
2607.	31-50	YFSKEEWEKMKASEKIFYVY	2607.02
1563.3	50-61	YMKRKYEAMTKL	1562.93
3989.9	31-61	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKL	3987.77
1603.74±1.53	51-63	MKRKYEAMTKLGF	1603.98
1766.45±1.5	50-63	YMKRKYEAMTKLGF	1767.16
1866.32±1.22	49-63	VYMKRKYEAMTKLGF	1866.29
4192.6	31-63	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGF	4192.00
4392.1	31-65**	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGFKA	4391.25

Boldface sequence correspond to peptides predicted to bind to MHC.

20 * On the basis of mass alone this peak could also have been assigned to the peptide 32-50, however proteasomal removal of just the N-terminal amino acid is unlikely. N-terminal sequencing (below) verifies the assignment to 31-49.

** On the basis of mass this fragment might also represent 33-68. N-terminal sequencing below is consistent with the assignment to 31-65.

25

Table 5. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO.	PEPTIDE	HLA	SYFPEITHI	NIH
11	FSKEWEKEM	B*3501	NP†	90
12	KMKASEKIF	B*08	17	<5
13 & (14)	(K)MKASEKIFY	A1	19 (19)	<5
15 & (16)	(M)KASEKIFYV	A*0201	22 (16)	1017
		B*08	17	<5
		B*5101	22 (13)	60
		B*5102	NP	133
		B*5103	NP	121
17 & (18)	(K)ASEKIFYVY	A1	34 (19)	14
19 & (20)	(K)RKYEAMTKL	A*0201	15	<5
		A26	15	NP
		B14	NP	45 (60)
		B*2705	21	15
		B*2709	16	NP
		B*5101	15	<5
21	KYEAMTKLGF	A1	16	<5
		A24	NP	300
22	YEAMTKLGF	B*4403	NP	80
23	EAMTKLGF	B*08	22	<5

†No prediction

As seen in Table 5, N-terminal addition of authentic sequence to epitopes can generate epitopes for the same or different MHC restriction elements. Note in particular the pairing of (K)RKYEAMTKL (SEQ ID NOS 19 and (20)) with HLA-B14, where the 10-mer has a longer predicted halftime of dissociation than the co-C-terminal 9-mer. Also note the case of the 10-mer KYEAMTKLGF (SEQ ID NO. 21) which can be used as a vaccine useful with several MHC types by relying on N-terminal trimming to create the epitopes for HLA-B*4403 and -B*08.

6. HLA-A0201 binding assay:

Binding of the candidate epitope KASEKIFYV, SSX-2₄₁₋₄₉, (SEQ ID NO. 15) to HLA-A2.1 was assayed using a modification of the method of Stauss et al., (Proc Natl Acad Sci USA 89(17):7871-5 (1992)). Specifically, T2 cells, which express empty or unstable MHC molecules on their surface, were washed twice with Iscove's modified Dulbecco's medium (IMDM) and cultured overnight in serum-free AIM-V medium (Life Technologies, Inc., Rockville, MD) supplemented with human β 2-microglobulin at 3 μ g/ml (Sigma, St. Louis, MO) and added peptide, at 800, 400, 200, 100, 50, 25, 12.5, and 6.25 μ g/ml in a 96-well flat-bottom plate at 3×10^5 cells/200 μ l (microliter)/well. Peptide was mixed with the cells by repipeting before distributing to the plate (alternatively peptide can be added to individual wells), and the plate was rocked gently for 2 minutes. Incubation was in a 5% CO₂ incubator at 37°C. The next day the unbound peptide was removed by washing twice with serum free RPMI medium and a saturating amount of anti-class I HLA monoclonal antibody, fluorescein isothiocyanate (FITC)-conjugated anti-HLA A2, A28 (One

Lambda, Canoga Park, CA) was added. After incubation for 30 minutes at 4°C, cells were washed 3 times with PBS supplemented with 0.5% BSA, 0.05%(w/v) sodium azide, pH 7.4-7.6 (staining buffer). (Alternatively W6/32 (Sigma) can be used as the anti-class I HLA monoclonal antibody the cells washed with staining buffer and then incubated with fluorescein isothiocyanate (FITC)-
 5 conjugated goat F(ab') antimouse-IgG (Sigma) for 30 min at 4°C and washed 3 times as before.) The cells were resuspended in 0.5 ml staining buffer. The analysis of surface HLA-A2.1 molecules stabilized by peptide binding was performed by flow cytometry using a FACScan (Becton Dickinson, San Jose, CA). If flow cytometry is not to be performed immediately the cells can be fixed by adding a quarter volume of 2% paraformaldehyde and storing in the dark at 4°C.

10 The results of the experiment are shown in Figure 5. SSX-2₄₁₋₄₉ (SEQ ID NO. 15) was found to bind HLA-A2.1 to a similar extent as the known A2.1 binder FLPSDYFPSV (HBV₁₈₋₂₇; SEQ ID NO: 24) used as a positive control. An HLA-B44 binding peptide, AEMGKYSFY (SEQ ID NO: 25), was used as a negative control. The fluorescence obtained from the negative control was similar to the signal obtained when no peptide was used in the assay. Positive and negative
 15 control peptides were chosen from Table 18.3.1 in *Current Protocols in Immunology* p. 18.3.2, John Wiley and Sons, New York, 1998.

7. Immunogenicity:

A. In vivo immunization of mice.

HHD1 transgenic A*0201 mice (Pascolo, S., et al. *J. Exp. Med.* 185:2043-2051, 1997)
 20 were anesthetized and injected subcutaneously at the base of the tail, avoiding lateral tail veins, using 100 µl containing 100 nmol of SSX-2₄₁₋₄₉ (SEQ ID NO. 15) and 20 µg of HTL epitope peptide in PBS emulsified with 50 µl of IFA (incomplete Freund's adjuvant).

B. Preparation of stimulating cells (LPS blasts).

Using spleens from 2 naive mice for each group of immunized mice, un-immunized mice
 25 were sacrificed and the carcasses were placed in alcohol. Using sterile instruments, the top dermal layer of skin on the mouse's left side (lower mid-section) was cut through, exposing the peritoneum. The peritoneum was saturated with alcohol, and the spleen was aseptically extracted. The spleen was placed in a petri dish with serum-free media. Splenocytes were isolated by using sterile plungers from 3 ml syringes to mash the spleens. Cells were collected in a 50 ml conical
 30 tubes in serum-free media, rinsing dish well. Cells were centrifuged (12000 rpm, 7 min) and washed one time with RPMI. Fresh spleen cells were resuspended to a concentration of 1x10⁶ cells per ml in RPMI-10%FCS (fetal calf serum). 25g/ml lipopolysaccharide and 7 µg/ml Dextran Sulfate were added. Cell were incubated for 3 days in T-75 flasks at 37°C, with 5% CO₂. Splenic blasts were collected in 50 ml tubes pelleted (12000 rpm, 7 min) and resuspended to 3X10⁷/ml in
 35 RPMI. The blasts were pulsed with the priming peptide at 50 µg/ml, RT 4hr. mitomycin C-treated at 25µg/ml, 37⁰C, 20 min and washed three times with DMEM.

C. In vitro stimulation.

3 days after LPS stimulation of the blast cells and the same day as peptide loading, the primed mice were sacrificed (at 14 days post immunization) to remove spleens as above. 3×10^6 splenocytes were co-cultured with 1×10^6 LPS blasts/well in 24-well plates at 37°C , with 5% CO_2 in DMEM media supplemented with 10% FCS, 5×10^{-5} M β -mercaptoethanol, 100 $\mu\text{g}/\text{ml}$ streptomycin and 100 IU/ml penicillin. Cultures were fed 5% (vol/vol) ConA supernatant on day 3 and assayed for cytolytic activity on day 7 in a ^{51}Cr -release assay.

D. Chromium-release assay measuring CTL activity.

To assess peptide specific lysis, 2×10^6 T2 cells were incubated with 100 μCi sodium chromate together with 50 $\mu\text{g}/\text{ml}$ peptide at 37°C for 1 hour. During incubation they were gently shaken every 15 minutes. After labeling and loading, cells were washed three times with 10 ml of DMEM-10% FCS, wiping each tube with a fresh Kimwipe after pouring off the supernatant. Target cells were resuspended in DMEM-10% FBS $1 \times 10^5/\text{ml}$. Effector cells were adjusted to $1 \times 10^7/\text{ml}$ in DMEM-10% FCS and 100 μl serial 3-fold dilutions of effectors were prepared in U-bottom 96-well plates. 100 μl of target cells were added per well. In order to determine spontaneous release and maximum release, six additional wells containing 100 μl of target cells were prepared for each target. Spontaneous release was revealed by incubating the target cells with 100 μl medium; maximum release was revealed by incubating the target cells with 100 μl of 2% SDS. Plates were then centrifuged for 5 min at 600 rpm and incubated for 4 hours at 37°C in 5% CO_2 and 80% humidity. After the incubation, plates were then centrifuged for 5 min at 1200 rpm. Supernatants were harvested and counted using a gamma counter. Specific lysis was determined as follows: % specific release = $[(\text{experimental release} - \text{spontaneous release})/(\text{maximum release} - \text{spontaneous release})] \times 100$.

Results of the chromium release assay demonstrating specific lysis of peptide pulsed target cells are shown in figure 6.

8. Cross-reactivity with other SSX proteins:

SSX-2₄₁₋₄₉ (SEQ ID NO. 15) shares a high degree of sequence identity with the same region of the other SSX proteins. The surrounding regions have also been generally well conserved. Thus the housekeeping proteasome can cleave following V₄₉ in all five sequences. Moreover, SSX₄₁₋₄₉ is predicted to bind HLA-A*0201 (see Table 6). CTL generated by immunization with SSX-2₄₁₋₄₉ cross-react with tumor cells expressing other SSX proteins.

Table 6. SSX₄₁₋₄₉ - A*0201 Predicted Binding

SEQ ID NO.	Family Member	Sequence	SYFPEITHI Score	NIH Score
15	SSX-2	KASEKIFYV	22	1017
26	SSX-1	KYSEKISYV	18	1.7
27	SSX-3	KVSEKIVYV	24	1105
28	SSX-4	KSSEKIVYV	20	82
29	SSX-5	KASEKIYV	22	175

Example 4Cluster Analysis (PSMA₁₆₃₋₁₉₂).

- 5 [0227] A peptide, AFSPQGMPEGDLVYVNYARTEDFFKLERDM, PSMA₁₆₃₋₁₉₂, (SEQ ID NO. 30), containing an A1 epitope cluster from prostate specific membrane antigen, PSMA₁₆₈₋₁₉₀ (SEQ ID NO. 31) was synthesized using standard solid-phase F-moc chemistry on a 433A ABI Peptide synthesizer. After side chain deprotection and cleavage from the resin, peptide first dissolved in formic acid and then diluted into 30% Acetic acid, was run on a reverse-phase
- 10 preparative HPLC C4 column at following conditions: linear AB gradient (5% B/min) at a flow rate of 4 ml/min, where eluent A is 0.1% aqueous TFA and eluent B is 0.1% TFA in acetonitrile. A fraction at time 16.642 min containing the expected peptide, as judged by mass spectrometry, was pooled and lyophilized. The peptide was then subjected to proteasome digestion and mass spectrum analysis essentially as described above. Prominent peaks from the mass spectra are
- 15 summarized in Table 7.

Table 7. PSMA₁₆₃₋₁₉₂ Mass Peak Identification.

PEPTIDE	SEQUENCE	CALCULATED MASS (MH ⁺)
163-177	AFSPQGMPEGDLVYV	1610.0
178-189	NYARTEDFFKLE	1533.68
170-189	PEGDLVYVNYARTEDFFKLE	2406.66
178-191	NYARTEDFFKLERD	1804.95
170-191	PEGDLVYVNYARTEDFFKLERD	2677.93
178-192	NYARTEDFFKLERDM	1936.17
163-176	AFSPQGMPEGDLVY	1511.70
177-192	VNYARTEDFFKLERDM	2035.30
163-179	AFSPQGMPEGDLVYVNY	1888.12
180-192	ARTEDFFKLERDM	1658.89
163-183	AFSPQGMPEGDLVYVNYARTE	2345.61
184-192	DDFKLERDM	1201.40
176-192	YVNYARTEDFFKLERDM	2198.48
167-185	QGMPEGDLVYVNYARTEDF	2205.41
178-186	NYARTEDFF	1163.22

Boldface sequences correspond to peptides predicted to bind to MHC, see Table 8.

N-terminal Pool Sequence Analysis

One aliquot at one hour of the proteasomal digestion (see Example 3 part 3 above) was subjected to N-terminal amino acid sequence analysis by an ABI 473A Protein Sequencer (Applied Biosystems, Foster City, CA). Determination of the sites and efficiencies of cleavage was based on
 5 consideration of the sequence cycle, the repetitive yield of the protein sequencer, and the relative yields of amino acids unique in the analyzed sequence. That is if the unique (in the analyzed sequence) residue X appears only in the nth cycle a cleavage site exists n-1 residues before it in the N-terminal direction. In addition to helping resolve any ambiguity in the assignment of mass to sequences, these data also provide a more reliable indication of the relative yield of the various
 10 fragments than does mass spectrometry.

For PSMA₁₆₃₋₁₉₂ (SEQ ID NO. 30) this pool sequencing supports a single major cleavage site after V₁₇₇ and several minor cleavage sites, particularly one after Y₁₇₉. Reviewing the results presented in figures 7A-C reveals the following:

- S at the 3rd cycle indicating presence of the N-terminus of the substrate.
- 15 Q at the 5th cycle indicating presence of the N-terminus of the substrate.
- N at the 1st cycle indicating cleavage after V₁₇₇.
- N at the 3rd cycle indicating cleavage after V₁₇₅. Note the fragment 176-192 in Table 7.
- T at the 5th cycle indicating cleavage after V₁₇₇.
- T at the 1st–3rd cycles, indicating increasingly common cleavages after R₁₈₁, A₁₈₀ and Y₁₇₉.
- 20 Only the last of these correspond to peaks detected by mass spectrometry; 163-179 and 180-192, see Table 7. The absence of the others can indicate that they are on fragments smaller than were examined in the mass spectrum.
- K at the 4th, 8th, and 10th cycles indicating cleavages after E₁₈₃, Y₁₇₉, and V₁₇₇, respectively, all of which correspond to fragments observed by mass spectroscopy. See Table 7.
- 25 A at the 1st and 3rd cycles indicating presence of the N-terminus of the substrate and cleavage after V₁₇₇, respectively.
- P at the 4th and 8th cycles indicating presence of the N-terminus of the substrate.
- G at the 6th and 10th cycles indicating presence of the N-terminus of the substrate.
- M at the 7th cycle indicating presence of the N-terminus of the substrate and/or cleavage
 30 after F₁₈₅.
- M at the 15th cycle indicating cleavage after V₁₇₇.
- The 1st cycle can indicate cleavage after D₁₉₁, see Table 7.
- R at the 4th and 13th cycle indicating cleavage after V₁₇₇.
- R at the 2nd and 11th cycle indicating cleavage after Y₁₇₉.
- 35 V at the 2nd, 6th, and 13th cycle indicating cleavage after V₁₇₅, M₁₆₉ and presence of the N-terminus of the substrate, respectively. Note fragments beginning at 176 and 170 in Table 7.

Y at the 1st, 2nd, and 14th cycles indicating cleavage after V₁₇₅, V₁₇₇, and presence of the N-terminus of the substrate, respectively.

L at the 11th and 12th cycles indicating cleavage after V₁₇₇, and presence of the N-terminus of the substrate, respectively, is the interpretation most consistent with the other data. Comparing to the mass spectrometry results we see that L at the 2nd, 5th, and 9th cycles is consistent with cleavage after F₁₈₆, E₁₈₃ or M₁₆₉, and Y₁₇₉, respectively. See Table 7.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further analysis. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include a predicted HLA-A1 binding sequence, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 8.

15 Table 8. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
32 & (33)	(G)MPEGDLVYV	A*0201	17 (27)	(2605)
		B*0702	20	<5
		B*5101	22	314
34 & (35)	(Q)GMPEGDLVY	A1	24 (26)	<5
		A3	16 (18)	36
		B*2705	17	25
		B*5101	15	NP†
36	MPEGDLVY			
37 & (38)	(P)EGDLVYVNY	A1	27 (15)	12
		A26	23 (17)	NP
39	LVYVNYARTE	A3	21	<5
40 & (41)	(Y)VNYARTEDF	A26	(20)	NP
		B*08	15	<5
		B*2705	12	50
42	NYARTEDFF	A24	NP†	100
		Cw*0401	NP	120
43	YARTEDFF	B*08	16	<5
44	RTEDFFKLE	A1	21	<5
		A26	15	NP

†No prediction

HLA-A*0201 binding assay:

HLA-A*0201 binding studies were performed with PSMA₁₆₈₋₁₇₇, GMPEGDLVYV, (SEQ ID NO. 33) essentially as described in Example 3 above. As seen in figure 8, this epitope exhibits significant binding at even lower concentrations than the positive control peptides. The Melan-A peptide used as a control in this assay (and throughout this disclosure), ELAIGILTV, is actually a variant of the natural sequence (EAAGIGILTV) and exhibits a high affinity in this assay.

Example 5Cluster Analysis (PSMA₂₈₁₋₃₁₀).

Another peptide, RGIAEAVGLPSIPVHPIGYYDAQKLEKMG, PSMA₂₈₁₋₃₁₀, (SEQ ID NO. 45), containing an A1 epitope cluster from prostate specific membrane antigen, PSMA₂₈₃₋₃₀₇ (SEQ ID NO. 46), was synthesized using standard solid-phase F-moc chemistry on a 433A ABI Peptide synthesizer. After side chain deprotection and cleavage from the resin, peptide in ddH₂O was run on a reverse-phase preparative HPLC C18 column at following conditions: linear AB gradient (5% B/min) at a flow rate of 4 ml/min, where eluent A is 0.1% aqueous TFA and eluent B is 0.1% TFA in acetonitrile. A fraction at time 17.061 min containing the expected peptide as judged by mass spectrometry, was pooled and lyophilized. The peptide was then subjected to proteasome digestion and mass spectrum analysis essentially as described above. Prominent peaks from the mass spectra are summarized in Table 9.

Table 9. PSMA₂₈₁₋₃₁₀ Mass Peak Identification.

PEPTIDE	SEQUENCE	CALCULATE D MASS (MH ⁺)
281-297	RGIAEAVGLPSIPVHPI*	1727.07
286-297	AVGLPSIPVHPI**	1200.46
287-297	VGLPSIPVHPI	1129.38
288-297	GLPSIPVHPI [†]	1030.25
298-310	GYDAQKLEKMG [‡]	1516.5
298-305	GYDAQKLS	958.05
281-305	RGIAEAVGLPSIPVHPIGYYDAQKL	2666.12
281-307	RGIAEAVGLPSIPVHPIGYYDAQKLE	2908.39
286-307	AVGLPSIPVHPIGYYDAQKLE [¶]	2381.78
287-307	VGLPSIPVHPIGYYDAQKLE	2310.70
288-307	GLPSIPVHPIGYYDAQKLE [#]	2211.57
281-299	RGIAEAVGLPSIPVHPIGY	1947
286-299	AVGLPSIPVHPIGY	1420.69
287-299	VGLPSIPVHPIGY	1349.61
288-299	GLPSIPVHPIGY	1250.48
287-310	VGLPSIPVHPIGYYDAQKLEKMG	2627.14
288-310	GLPSIPVHPIGYYDAQKLEKMG	2528.01

Boldface sequences correspond to peptides predicted to bind to MHC, see Table 10.

*By mass alone this peak could also have been 296-310 or 288-303.

**By mass alone this peak could also have been 298-307. Combination of HPLC and mass spectrometry show that at some later time points this peak is a mixture of both species.

[†] By mass alone this peak could also have been 289-298.

[‡] By mass alone this peak could also have been 281-295 or 294-306.

[§] By mass alone this peak could also have been 297-303.

[¶] By mass alone this peak could also have been 285-306.

[#] By mass alone this peak could also have been 288-303.

None of these alternate assignments are supported N-terminal pool sequence analysis.

N-terminal Pool Sequence Analysis

One aliquot at one hour of the proteasomal digestion (see Example 3 part 3 above) was subjected to N-terminal amino acid sequence analysis by an ABI 473A Protein Sequencer (Applied Biosystems, Foster City, CA). Determination of the sites and efficiencies of cleavage was based on consideration of the sequence cycle, the repetitive yield of the protein sequencer, and the relative yields of amino acids unique in the analyzed sequence. That is if the unique (in the analyzed sequence) residue X appears only in the nth cycle a cleavage site exists n-1 residues before it in the N-terminal direction. In addition to helping resolve any ambiguity in the assignment of mass to sequences, these data also provide a more reliable indication of the relative yield of the various fragments than does mass spectrometry.

For PSMA₂₈₁₋₃₁₀ (SEQ ID NO. 45) this pool sequencing supports two major cleavage sites after V₂₈₇ and I₂₉₇ among other minor cleavage sites. Reviewing the results presented in Fig. 9 reveals the following:

S at the 4th and 11th cycles indicating cleavage after V₂₈₇ and presence of the N-terminus of the substrate, respectively.

H at the 8th cycle indicating cleavage after V₂₈₇. The lack of decay in peak height at positions 9 and 10 versus the drop in height present going from 10 to 11 can suggest cleavage after A₂₈₆ and E₂₈₅ as well, rather than the peaks representing latency in the sequencing reaction.

D at the 2nd, 4th, and 7th cycles indicating cleavages after Y₂₉₉, I₂₉₇, and V₂₉₄, respectively. This last cleavage is not observed in any of the fragments in Table 10 or in the alternate assignments in the notes below.

Q at the 6th cycle indicating cleavage after I₂₉₇.

M at the 10th and 12th cycle indicating cleavages after Y₂₉₉ and I₂₉₇, respectively.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include a predicted HLA-A1 binding sequence, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 10.

Table 10.

Predicted HLA binding by proteasomally generated fragments: PSMA₂₈₁₋₃₁₀

SEQ ID NO.	PEPTIDE	HLA	SYFPEITHI	NIH
47 & (48)	(G)LPSPVHPI	A*0201	16 (24)	(24)
		B*0702/B7	23	12
		B*5101	24	572
		Cw*0401	NP†	20
49 & (50)	(P)IGYYDAQKL	A*0201	(16)	<5
		A26	(20)	NP
		B*2705	16	25
		B*2709	15	NP
		B*5101	21	57
		Cw*0301	NP	24
51 & (52)	(P)SIPVHPIGY	A1	21 (27)	<5
		A26	22	NP
		A3	16	<5
		B*5101	16	NP
53	IPVHPIGY			
54	YYDAQKLE	A1	22	<5

†No prediction

- 5 As seen in Table 10, N-terminal addition of authentic sequence to epitopes can often generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (G)LPSPVHPI with HLA-A*0201, where the 10-mer can be used as a vaccine useful with several MHC types by relying on N-terminal trimming to create the epitopes for HLA-B7, -B*5101, and Cw*0401.

10 HLA-A*0201 binding assay:

HLA-A*0201 binding studies were performed with PSMA₂₈₈₋₂₉₇, GLPSIPVHPI, (SEQ ID NO. 48) essentially as described in Examples 3 and 4 above. As seen in figure 8, this epitope exhibits significant binding at even lower concentrations than the positive control peptides.

Example 6

15 Cluster Analysis (PSMA₄₅₄₋₄₈₁).

Another peptide, SSIEGNYTLRV DCTPLMYSLVHLTKEL, PSMA₄₅₄₋₄₈₁, (SEQ ID NO. 55) containing an epitope cluster from prostate specific membrane antigen, was synthesized by MPS (purity >95%) and subjected to proteasome digestion and mass spectrum analysis as described above. Prominent peaks from the mass spectra are summarized in Table 11.

20

Table 11. PSMA₄₅₄₋₄₈₁ Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH ⁺)
1238.5	454-464	SSIEGNYTLRV	1239.78

1768.38±0.60	454-469	SSIEGNYTLRV DCTPL	1768.99
1899.8	454-470	SSIEGNYTLRV DCTPLM	1900.19
1097.63±0.91	463-471	RVDCTPLMY	1098.32
2062.87±0.68	454-471*	SSIEGNYTLRV DCTPLMY	2063.36
1153	472-481**	SLVHNLTKEL	1154.36
1449.93±1.79	470-481	MYSLVHNLTKEL	1448.73

Boldface sequence correspond to peptides predicted to bind to MHC, see Table 12.

* On the basis of mass alone this peak could equally well be assigned to the peptide 455-472 however proteasomal removal of just the N-terminal amino acid is considered unlikely. If the issue were important it could be resolved by N-terminal sequencing.

**On the basis of mass this fragment might also represent 455-464.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1 binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 12.

Table 12. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
56 & (57)	(S) IEGNYTLRV	A1	(19)	<5
58	EGNYTLRV	A*0201	16 (22)	<5
		B*5101	15	NP†
59 & (60)	(Y) TLRVDCTPL	A*0201	20 (18)	(5)
		A26	16 (18)	NP
		B7	14	40
		B8	23	<5
		B*2705	12	30
		Cw*0301	NP	(30)
		B*2705	20	600
61	LRVDCTPLM	B*2709	20	NP
		A1	32 (22)	125 (13.5)
62 & (63)	(L) RVDCTPLMY	A3	25	<5
		A26	22	NP
		B*2702	NP	(200)
		B*2705	13 (NP)	(1000)

†No prediction

As seen in Table 12, N-terminal addition of authentic sequence to epitopes can often generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (L)RVDCTPLMY (SEQ ID NOS 62 and (63)) with HLA-B*2702/5, where the 10-mer has substantial predicted halftimes of dissociation and the co-C-

terminal 9-mer does not. Also note the case of SIEGNYTLRV (SEQ ID NO 57) a predicted HLA-A*0201 epitope which can be used as a vaccine useful with HLA-B*5101 by relying on N-terminal trimming to create the epitope.

HLA-A*0201 binding assay

5 HLA-A*0201 binding studies were preformed, essentially as described in Example 3 above, with PSMA₄₆₀₋₄₆₉, TLRVDCTPL, (SEQ ID NO. 60). As seen in figure 10, this epitope was found to bind HLA-A2.1 to a similar extent as the known A2.1 binder FLPSDYFPSV (HBV₁₈₋₂₇; SEQ ID NO: 24) used as a positive control. Additionally, PSMA₄₆₁₋₄₆₉, (SEQ ID NO. 59) binds nearly as well.

10 ELISPOT analysis: PSMA₄₆₃₋₄₇₁ (SEQ ID NO. 62)

The wells of a nitrocellulose-backed microtiter plate were coated with capture antibody by incubating overnight at 4°C using 50 µl (microliter)/well of 4µg/ml murine anti-human γ (gamma)-IFN monoclonal antibody in coating buffer (35 mM sodium bicarbonate, 15 mM sodium carbonate, pH 9.5). Unbound antibody was removed by washing 4 times 5 min. with PBS. Unbound sites on
15 the membrane then were blocked by adding 200µl (microliter)/well of RPMI medium with 10% serum and incubating 1 hr. at room temperature. Antigen stimulated CD8⁺ T cells, in 1:3 serial dilutions, were seeded into the wells of the microtiter plate using 100µl (microliter)/well, starting at 2x10⁵ cells/well. (Prior antigen stimulation was essentially as described in Scheibenbogen, C. et al. *Int. J. Cancer* 71:932-936, 1997. PSMA₄₆₂₋₄₇₁ (SEQ ID NO. 62) was added to a final
20 concentration of 10µg/ml and IL-2 to 100 U/ml and the cells cultured at 37°C in a 5% CO₂, water-saturated atmosphere for 40 hrs. Following this incubation the plates were washed with 6 times 200 µl (microliter)/well of PBS containing 0.05% Tween-20 (PBS-Tween). Detection antibody, 50µl (microliter)/well of 2g/ml biotinylated murine anti-human γ (gamma)-IFN monoclonal antibody in PBS+10% fetal calf serum, was added and the plate incubated at room temperature for
25 2 hrs. Unbound detection antibody was removed by washing with 4 times 200 µl of PBS-Tween. 100µl of avidin-conjugated horseradish peroxidase (Pharmingen, San Diego, CA) was added to each well and incubated at room temperature for 1 hr. Unbound enzyme was removed by washing with 6 times 200 µl of PBS-Tween. Substrate was prepared by dissolving a 20 mg tablet of 3-amino 9-ethylcoarbasole in 2.5 ml of N, N-dimethylformamide and adding that solution to 47,5 ml of 0.05
30 M phosphate-citrate buffer (pH 5.0). 25 µl of 30% H₂O₂ was added to the substrate solution immediately before distributing substrate at 100 µl (microliter)/well and incubating the plate at room temperature. After color development (generally 15-30 min.), the reaction was stopped by washing the plate with water. The plate was air dried and the spots counted using a stereomicroscope.

35 Figure 11 shows the detection of PSMA₄₆₃₋₄₇₁ (SEQ ID NO. 62)-reactive HLA-A1⁺ CD8⁺ T cells previously generated in cultures of HLA-A1⁺ CD8⁺ T cells with autologous dendritic cells

plus the peptide. No reactivity is detected from cultures without peptide (data not shown). In this case it can be seen that the peptide reactive T cells are present in the culture at a frequency between 1 in 2.2×10^4 and 1 in 6.7×10^4 . That this is truly an HLA-A1-restricted response is demonstrated by the ability of anti-HLA-A1 monoclonal antibody to block γ (gamma) IFN production; see figure 12.

5 Example 7

Cluster Analysis (PSMA₆₅₃₋₆₈₇).

Another peptide, FDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRP FY PSMA₆₅₃₋₆₈₇, (SEQ ID NO. 64) containing an A2 epitope cluster from prostate specific membrane antigen, PSMA₆₆₀₋₆₈₁ (SEQ ID NO 65), was synthesized by MPS (purity >95%) and subjected to proteasome
10 digestion and mass spectrum analysis as described above. Prominent peaks from the mass spectra are summarized in Table 13.

Table 13. PSMA₆₅₃₋₆₈₇ Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH ⁺)
906.17±0.65	681-687**	LPDRPFY	908.05
1287.73±0.76	677-687**	DPLGLPDRPFY	1290.47
1400.3±1.79	676-687	IDPLGLPDRPFY	1403.63
1548.0±1.37	675-687	FIDPLGLPDRPFY	1550.80
1619.5±1.51	674-687**	AFIDPLGLPDRPFY	1621.88
1775.48±1.32	673-687*	RAFIDPLGLPDRPFY	1778.07
2440.2±1.3	653-672	FDKSNPIVLRMMNDQLMFLE	2442.93
1904.63±1.56	672-687*	ERAFIDPLGLPDRPFY	1907.19
2310.6±2.5	653-671	FDKSNPIVLRMMNDQLMFL	2313.82
2017.4±1.94	671-687	LERAFIDPLGLPDRPFY	2020.35
2197.43±1.78	653-670	FDKSNPIVLRMMNDQLMF	2200.66

15 **Boldface** sequence correspond to peptides predicted to bind to MHC, see Table 13.

* On the basis of mass alone this peak could equally well be assigned to a peptide beginning at 654, however proteasomal removal of just the N-terminal amino acid is considered unlikely. If the issue were important it could be resolved by N-terminal sequencing.

20 ** On the basis of mass alone these peaks could have been assigned to internal fragments, but given the overall pattern of digestion it was considered unlikely.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction
25 steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1

binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 14.

Table 14. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
66 & (67)	(R)MMNDQLMF L	A*0201	24 (23)	1360 (722)
		A*0205	NP†	71 (42)
		A26	15	NP
		B*2705	12	50
68	RMMNDQLMF	B*2705	17	75

†No prediction

As seen in Table 14, N-terminal addition of authentic sequence to epitopes can generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (R)MMNDQLMFL (SEQ ID NOS. 66 and (67)) with HLA-A*02, where the 10-mer retains substantial predicted binding potential.

HLA-A*0201 binding assay

HLA-A*0201 binding studies were preformed, essentially as described in Example 3 above, with PSMA₆₆₃₋₆₇₁, (SEQ ID NO. 66) and PSMA₆₆₂₋₆₇₁, RMMNDQLMFL (SEQ NO. 67). As seen in figures 10, 13 and 14, this epitope exhibits significant binding at even lower concentrations than the positive control peptide (FLPSDYFPSV (HBV₁₈₋₂₇); SEQ ID NO: 24). Though not run in parallel, comparison to the controls suggests that PSMA₆₆₂₋₆₇₁ (which approaches the Melan A peptide in affinity) has the superior binding activity of these two PSMA peptides.

Example 8

Vaccinating with epitope vaccines.

1. Vaccination with peptide vaccines:

A. Intranodal delivery

A formulation containing peptide in aqueous buffer with an antimicrobial agent, an antioxidant, and an immunomodulating cytokine, was injected continuously over several days into the inguinal lymph node using a miniature pumping system developed for insulin delivery (MiniMed; Northridge, CA). This infusion cycle was selected in order to mimic the kinetics of antigen presentation during a natural infection.

B. Controlled release

A peptide formulation is delivered using controlled PLGA microspheres as is known in the art, which alter the pharmacokinetics of the peptide and improve immunogenicity. This formulation is injected or taken orally.

C. Gene gun delivery

5 A peptide formulation is prepared wherein the peptide is adhered to gold microparticles as is known in the art. The particles are delivered in a gene gun, being accelerated at high speed so as to penetrate the skin, carrying the particles into dermal tissues that contain pAPCs.

D. Aerosol delivery

10 A peptide formulation is inhaled as an aerosol as is known in the art, for uptake into appropriate vascular or lymphatic tissue in the lungs.

2. Vaccination with nucleic acid vaccines:

15 A nucleic acid vaccine is injected into a lymph node using a miniature pumping system, such as the MiniMed insulin pump. A nucleic acid construct formulated in an aqueous buffered solution containing an antimicrobial agent, an antioxidant, and an immunomodulating cytokine, is delivered over a several day infusion cycle in order to mimic the kinetics of antigen presentation during a natural infection.

Optionally, the nucleic acid construct is delivered using controlled release substances, such as PLGA microspheres or other biodegradable substances. These substances are injected or taken orally. Nucleic acid vaccines are given using oral delivery, priming the immune response through uptake into GALT tissues. Alternatively, the nucleic acid vaccines are delivered using a gene gun, wherein the nucleic acid vaccine is adhered to minute gold particles. Nucleic acid constructs can also be inhaled as an aerosol, for uptake into appropriate vascular or lymphatic tissue in the lungs.

Example 9

Assays for the effectiveness of epitope vaccines.

25 1. Tetramer analysis:

Class I tetramer analysis is used to determine T cell frequency in an animal before and after administration of a housekeeping epitope. Clonal expansion of T cells in response to an epitope indicates that the epitope is presented to T cells by pAPCs. The specific T cell frequency is measured against the housekeeping epitope before and after administration of the epitope to an animal, to determine if the epitope is present on pAPCs. An increase in frequency of T cells specific to the epitope after administration indicates that the epitope was presented on pAPC.

2. Proliferation assay:

35 Approximately 24 hours after vaccination of an animal with housekeeping epitope, pAPCs are harvested from PBMCs, splenocytes, or lymph node cells, using monoclonal antibodies against specific markers present on pAPCs, fixed to magnetic beads for affinity purification. Crude blood or splenocyte preparation is enriched for pAPCs using this technique. The enriched pAPCs are

then used in a proliferation assay against a T cell clone that has been generated and is specific for the housekeeping epitope of interest. The pAPCs are coincubated with the T cell clone and the T cells are monitored for proliferation activity by measuring the incorporation of radiolabeled thymidine by T cells. Proliferation indicates that T cells specific for the housekeeping epitope are being stimulated by that epitope on the pAPCs.

3. Chromium release assay:

A human patient, or non-human animal genetically engineered to express human class I MHC, is immunized using a housekeeping epitope. T cells from the immunized subject are used in a standard chromium release assay using human tumor targets or targets engineered to express the same class I MHC. T cell killing of the targets indicates that stimulation of T cells in a patient would be effective at killing a tumor expressing a similar TuAA.

Example 10

Induction of CTL response with naked DNA is efficient by Intra-lymph node immunization.

In order to quantitatively compare the CD8⁺ CTL responses induced by different routes of immunization a plasmid DNA vaccine (pEGFP-L33A) containing a well-characterized immunodominant CTL epitope from the LCMV-glycoprotein (G) (gp33; amino acids 33-41) (Oehen, S., et al., *Immunology* 99, 163-169 2000) was used, as this system allows a comprehensive assessment of antiviral CTL responses. Groups of 2 C57BL/6 mice were immunized once with titrated doses (200-0.02µg) of pEGFP-L33A DNA or of control plasmid pEGFP-N3, administered i.m. (intramuscular), i.d. (intradermal), i.spl. (intrasplenic), or i.ln. (intra-lymph node). Positive control mice received 500 pfu LCMV i.v. (intravenous). Ten days after immunization spleen cells were isolated and gp33-specific CTL activity was determined after secondary *in vitro* restimulation. As shown in Fig. 15, i.m. or i.d. immunization induced weakly detectable CTL responses when high doses of pEGFP-L33A DNA (200µg) were administered. In contrast, potent gp33-specific CTL responses were elicited by immunization with only 2µg pEGFP-L33A DNA i.spl. and with as little as 0.2µg pEGFP-L33A DNA given i.ln. (figure 15; symbols represent individual mice and one of three similar experiments is shown). Immunization with the control pEGFP-N3 DNA did not elicit any detectable gp33-specific CTL responses (data not shown).

Example 11

Intra-lymph node DNA immunization elicits anti-tumor immunity.

To examine whether the potent CTL responses elicited following i.ln. immunization were able to confer protection against peripheral tumors, groups of 6 C57BL/6 mice were immunized three times at 6-day intervals with 10µg of pEGFP-L33A DNA or control pEGFP-N3 DNA. Five days after the last immunization small pieces of solid tumors expressing the gp33 epitope (EL4-33) were transplanted s.c. into both flanks and tumor growth was measured every 3-4d. Although the

EL4-33 tumors grew well in mice that had been repetitively immunized with control pEGFP-N3 DNA (figure 16), mice which were immunized with pEFGPL33A DNA i.ln. rapidly eradicated the peripheral EL4-33 tumors (figure 16).

Example 12

- 5 Differences in lymph node DNA content mirrors differences in CTL response following intra-lymph node and intramuscular injection.

pEFGPL33A DNA was injected i.ln. or i.m. and plasmid content of the injected or draining lymph node was assessed by real time PCR after 6, 12, 24, 48 hours, and 4 and 30 days. At 6, 12, and 24 hours the plasmid DNA content of the injected lymph nodes was approximately three orders
10 of magnitude greater than that of the draining lymph nodes following i.m. injection. No plasmid DNA was detectable in the draining lymph node at subsequent time points (Fig. 17). This is consonant with the three orders of magnitude greater dose needed using i.m. as compared to i.ln. injections to achieve a similar levels of CTL activity. CD8^{-/-} knockout mice, which do not develop a CTL response to this epitope, were also injected i.ln. showing clearance of DNA from the lymph
15 node is not due to CD8⁺ CTL killing of cells in the lymph node. This observation also supports the conclusion that i.ln. administration will not provoke immunopathological damage to the lymph node.

Example 13

Administration of a DNA plasmid formulation of a therapeutic vaccine for melanoma to humans.

20 A SYNCHROTOPE™ TA2M melanoma vaccine encoding the HLA-A2-restricted tyrosinase epitope SEQ ID NO. 1 and epitope cluster SEQ ID NO. 69, was formulated in 1% Benzyl alcohol, 1% ethyl alcohol, 0.5mM EDTA, citrate-phosphate, pH 7.6. Aliquots of 80, 160, and 320 µg DNA/ml were prepared for loading into MINIMED 407C infusion pumps. The catheter of a SILHOUETTE infusion set was placed into an inguinal lymph node visualized by
25 ultrasound imaging. The assembly of pump and infusion set was originally designed for the delivery of insulin to diabetics and the usual 17mm catheter was substituted with a 31mm catheter for this application. The infusion set was kept patent for 4 days (approximately 96 hours) with an infusion rate of about 25 µl (microliter)/hour resulting in a total infused volume of approximately 2.4 ml. Thus the total administered dose per infusion was approximately 200, and 400 µg; and can
30 be 800 µg, respectively, for the three concentrations described above. Following an infusion subjects were given a 10 day rest period before starting a subsequent infusion. Given the continued residency of plasmid DNA in the lymph node after administration (as in example 12) and the usual kinetics of CTL response following disappearance of antigen, this schedule will be sufficient to maintain the immunologic CTL response.

- 35 Example 14

Evaluating Likelihood of Epitope Cross-reactivity on Non-target Tissues.

As noted above PSA is a member of the kallikrein family of proteases, which is itself a subset of the serine protease family. While the members of this family sharing the greatest degree of sequence identity with PSA also share similar expression profiles, it remains possible that individual epitope sequences might be shared with proteins having distinctly different expression profiles. A first step in evaluating the likelihood of undesirable cross-reactivity is the identification of shared sequences. One way to accomplish this is to conduct a BLAST search of an epitope sequence against the SWISSPROT or Entrez non-redundant peptide sequence databases using the "Search for short nearly exact matches" option; hypertext transfer protocol accessible on the world wide web (<http://www.ncbi.nlm.nih.gov/blast/index.html>). Thus searching SEQ ID NO. 104, WVLTAAHCI, against SWISSPROT (limited to entries for homo sapiens) one finds four exact matches, including PSA. The other three are from kallikrein 1 (tissue kallikrein), and elastase 2A and 2B. While these nine amino acid segments are identical, the flanking sequences are quite distinct, particularly on the C-terminal side, suggesting that processing may proceed differently and that thus the same epitope may not be liberated from these other proteins. (Please note that kallikrein naming is confused. Thus, the kallikrein 1 [accession number P06870] is a different protein than the one [accession number AAD13817] mentioned in the paragraph on PSA above in the section on tumor-associated antigens).

This possibility can be tested in several ways. Synthetic peptides containing the epitope sequence embedded in the context of each of these proteins can be subjected to *in vitro* proteasomal digestion and analysis as described above. Alternatively, cells expressing these other proteins, whether by natural or recombinant expression, can be used as targets in a cytotoxicity (or similar) assay using CD8⁺ T cells that recognize the epitope, in order to determine if the epitope is processed and presented.

Examples 15-67

Epitopes.

The methodologies described above, and in particular in examples 3-7, have been applied to additional synthetic peptide substrates, as summarized in figures 18-70 leading to the identification of further epitopes as set forth in tables 15-67 below. The substrates used here were generally designed to identify products of housekeeping proteasomal processing that give rise to HLA-A*0201 binding epitopes, but additional MHC-binding reactivities can be predicted, as discussed above. Many such reactivities are disclosed, however, these listings are meant to be exemplary, not exhaustive or limiting. As also discussed above, individual components of the analyses can be used in varying combinations and orders. N-terminal pool sequencing which allows quantitation of various cleavages and can resolve ambiguities in the mass spectrum where necessary, can also be used to identify cleavage sites when digests of substrate yield fragments that do not fly well in MALDI-TOF mass spectrometry. Due to these advantages it was routinely used.

Although it is preferred to identify epitopes on the basis of the C-terminus of an observed fragment, epitopes can also be identified on the basis of the N-terminus of an observed fragment adjacent to the epitope.

Not all of the substrates necessarily meet the formal definition of an epitope cluster as referenced in example 3. Some clusters are so large that it was more convenient to use substrates spanning only a portion of the cluster. In other cases, substrates were extended beyond clusters meeting the formal definition to include neighboring predicted epitopes or were designed around predicted epitopes with no association with any cluster. In some instances, actual binding activity dictated what substrate was made when HLA binding activity was determined for a selection of peptides with predicted affinity, before synthetic substrates were designed.

Figures 18-70 show the results of proteasomal digestion analysis as a mapping of mass spectrum peaks onto the substrate sequence. Each figure presents an individual timepoint from the digestion judged to be representative of the overall data, however some epitopes listed in Tables 15-67 were identified based on fragments not observed at the particular timepoints illustrated. The mapping of peaks onto the sequence was informed by N-terminal pool sequencing of the digests, as noted above. Peaks possibly corresponding to more than one fragment are represented by broken lines. Nonetheless, epitope identifications are supported by unambiguous occurrence of the associated cleavage.

Example 15: Tyrosinase 171-203Table 15Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
171-179	NIYDLFVWM	108	A0201	17	93.656
			A26	25	N/A
			A3	18	<5
173-182	YDLFVWMHYY	109	A1	17	<5
174-182	DLFVWMHYY	110	A1	16	<5
			A26	30	N/A
			A3	16	27
186-194	DALLGGSEI	111	A0201	17	<5
			B5101	26	440
191-200	GSEIWRDIDF	112	A1	18	67.5
192-200	SEIWRDIDF	113	B08	16	<5
193-201	EIWRDIDFA	114	A26	20	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 18.

5

Example 16: Tyrosinase 401-427Table 16Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
407-416	LQEVYPEANA	115	A0203	18	N/A
409-418	EVYPEANAPI	116	A26	19	N/A
			A3	20	<5
410-418	VYPEANAPI	117	B5101	15	6.921
411-418	YPEANAPI	118	B5101	22	N/A
411-420	YPEANAPIGH	119	A1	16	<5
416-425	APIGHNRESY	120	A1	18	<5
			A26	15	N/A
417-425	PIGHNRESY	121	A1	16	<5
			A26	21	N/A
			A3	17	<5
417-426	PIGHNRESYM	122	A26	19	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 19.

10

Example 17: Tyrosinase 415-449Table 17Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
416-425	APIGHNRESY	120	A1	18	<5
			A26	15	N/A
			A3	17	<5
			B0702	15	N/A
417-425	PIGHNRESY	124	A1	16	<5
			A26	21	N/A
			A3	17	<5
423-430	ESYMVPFI	125	B5101	17	N/A
423-432	ESYMVPFIPL	126	A26	18	N/A
424-432	SYMVPFIPL	127	B0702	16	N/A
424-433	SYMVPFIPLY	128	A1	19	<5
			A26	15	N/A
425-433	YMVPFIPLY	129	A0201	18	<5
			A1	23	5
			A26	17	N/A
426-434	MVPFIPLYR	130	A3	18	<5
426-435	MVPFIPLYRN	131	A26	16	N/A
427-434	VPFIPLYR	132	B5101	18	N/A
430-437	IPLYRNGD	133	B08	16	<5
430-439	IPLYRNGDFF	134	B0702	18	N/A
431-439	PLYRNGDFF	135	A26	18	N/A
			A3	24	<5
431-440	PLYRNGDFFI	136	A0201	16	23.43
			A3	17	<5
434-443	RNGDFFISSK	137	A3	20	<5
435-443	NGDFFISSK	138	A3	15	<5
			B2705	15	5

5 †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 20.

Example 18: Tyrosinase 457-484Table 18Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
463-471	YIKSYLEQA	139	A0201	18	<5
			A26	17	N/A
466-474	SYLEQASRI	140	B5101	16	<5
469-478	EQASRIWSWL	141	A26	17	N/A
470-478	QASRIWSWL	142	B5101	16	55
471-478	ASRIWSWL	143	B08	16	<5
471-479	ASRIWSWLL	144	B08	16	<5
473-481	RIWSWLLGA	145	A0201	19	13.04
			A26	16	N/A
			A3	15	<5

10 †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 21.

Example 19: CEA 92-118Table 19Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
92-100	GPAYSGREI	146	B0702	18	8
			B08	15	<5
			B5101	22	484
92-101	GPAYSGREII	147	B0702	18	12
93-100	PAYSGREI	148	B5101	22	N.A.
93-101	PAYSGREII	149	B5101	24	48.4
93-102	PAYSGREIY	150	A1	19	<5
94-102	AYSGREIY	151	A1	21	<5
97-105	GREIYPNA	152	B2705	17	200
			B2709	16	
98-107	REIYPNASL	153	A0201	16	<5
99-107	EIIYPNASL	154	A0201	21	<5
			A26	28	N.A.
			A3	16	<5
			B0702	15	6
			B08	18	<5
			B2705	16	<5
99-108	EIIYPNASLL	155	A0201	16	<5
			A26	27	N.A.
			A3	17	<5
100-107	IYPNASL	156	B08	15	<5
100-108	IYPNASLL	157	A0201	23	15.979
			A26	21	N.A.
			A24	N.A.	<5
			A3	23	<5
			B08	15	<5
			B1510	15	N.A.
			B2705	16	50
100-109	IYPNASLLI	158	B2709	15	
			A0201	22	7.804
102-109	YPNASLLI	159	A3	20	<5
			B5101	23	N.A.
107-116	LLIQNIQND	160	A0201	18	<5
			A26	17	N.A.

5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 22.

Example 20: CEA 131-159Table 20Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
132-141	EEATGQFRVY	161	A1	19	<5
			A26	21	N.A.
133-141	EATGQFRVY	162	A1	22	<5
			A26	23	N.A.
			B5101	16	<5
141-149	YPELPKPSI	163	B0702	20	<5
			B5101	22	572
142-149	PELPKPSI	164	B08	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 23.

5

Example 21: CEA 225-251Table 21Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
225-233	RSDSVILNV	165	A0201	15	<5
			A1	22	<5
			B2709	15	N.A.
225-234	RSDSVILNVL	166	A0201	15	<5
226-234	SDSVILNVL	167	A0201	17	<5
226-235	SDSVILNVLY	168	A1	20	<5
227-235	DSVILNVLY	169	A1	22	<5
			A26	18	N.A.
233-242	VLYGPDAPTI	170	A0201	25	56.754
			A3	23	<5
234-242	LYGPDAPTI	171	A0201	15	<5
			B5101	15	5.72
235-242	YGPDAPI	172	B5101	22	N.A.
236-245	GPDAPTISPL	173	A0201	15	<5
			B0702	23	24
237-245	PDAPTISPL	174	A0201	15	<5
			A26	16	N.A.
			B2705	15	<5
238-245	DAPTISPL	175	B5101	25	N.A.
239-247	APTISPLNT	176	B0702	20	6
240-249	PTISPLNTSY	177	A1	22	<5
			A26	24	N.A.
241-249	TISPLNTSY	178	A1	20	5
			A26	24	N.A.
			A3	20	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 24.

10

Example 22: CEA 239-270Table 22Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
240-249	PTISPLNTSY	179	A1	22	<5
			A26	24	N.A.
241-249	TISPLNTSY	180	A1	20	5
			A26	24	N.A.
			A3	20	<5
246-255	NTSYRSGENL	181	A26	19	N.A.
247-255	TSYRSGENL	182	B2705	15	50
248-255	SYRSGENL	183	B08	18	<5
248-257	SYRSGENLNL	184	B0702	14	<5
249-257	YRSGENLNL	185	A0201	15	<5
			B0702	16	<5
			B2705	27	2000
			B2709	22	N.A.
251-259	SGENLNLSC	186	A1	19	<5
253-262	ENLNLSCHAA	187	A0203	19	<5
254-262	NLNLSCHAA	188	A0201	17	<5

5 †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 25.

Example 23: CEA 259-28610 Table 23Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
260-269	HAASNPPAQY	189	A1	15	<5
261-269	AASNPPAQY	190	A1	17	<5
			A3	17	<5
264-273	NPPAQYSWFV	191	B0702	18	<5
265-273	PPAQYSWFV	192	B0702	18	<5
			B5101	19	20
266-273	PAQYSWFV	193	B5101	18	N.A.
272-280	FVNGTFQQS	194	A26	18	N.A.
			A3	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 26.

Example 24: CEA 309-336Table 24Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
310-319	RTTVTTITVY	195	A1	22	<5
			A26	24	N.A.
			A3	15	<5
311-319	TTVTTITVY	196	A1	22	<5
			A26	24	N.A.
			B2705	15	5
319-327	YAEPPKPFIT	197	A0201	17	<5
			A1	17	18
			B5101	22	286
319-328	YAEPPKPFIT	198	A1	16	45
320-327	AEPPKPFIT	199	B08	16	<5
321-328	EPPKPFIT	200	B5101	16	N.A.
321-329	EPPKPFITS	201	B0702	16	<5
			B5101	16	12.1
322-329	PPKPFITS	202	B08	16	<5

5 †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 27.

Example 25: CEA 381-408Table 2510 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
382-391	SVTRNDVGPY	203	A1	18	<5
			A26	24	N.A.
			A3	21	<5
383-391	VTRNDVGPY	204	A1	23	<5
			A26	24	N.A.
389-397	GPYECGIQN	205	B5101	17	11
391-399	YECGIQNEL	206	A0201	17	<5
			B2705	17	30
394-402	GIQNELSVD	207	A26	15	N.A.
			A3	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 28.

Example 26: CEA 403-429Table 265 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
403-411	HSDPVILNV	208	A0201	17	<5
			A1	26	37.5
403-412	HSDPVILNVL	209	A0201	17	<5
			A1	19	7.5
			A26	15	N.A.
			A24	N.A.	8.064
			B4402	17	N.A.
404-412	SDPVILNVL	210	A0201	17	<5
			B4402	16	N.A.
404-413	SDPVILNVLY	211	A1	20	<5
405-412	DPVILNVL	212	B08	16	<5
			B5101	24	N.A.
405-413	DPVILNVLY	213	A1	18	<5
			A26	18	N.A.
			B5101	16	7.26
408-417	ILNVLYGPDD	214	A3	15	<5
411-420	VLYGPDDPTI	215	A0201	25	56.754
			A3	20	<5
412-420	LYGPDDPTI	216	A0201	15	<5
			A24	N.A.	60
413-420	YGPDDPTI	217	B5101	22	N.A.
417-425	DPTISPSYT	218	B0702	16	<5
418-427	PTISPSYTTY	219	A1	21	<5
			A26	27	N.A.
419-427	TISPSYTTY	220	A1	19	5
			A26	27	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 29.

Example 27: CEA 416-448Table 27Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
418-427	PTISPSYTTY	221	A1	21	<5
			A26	27	N.A.
419-427	TISPSYTTY	222	A1	19	5
			A26	27	N.A.
			A3	18	<5
419-428	TISPSYTYR	223	A3	15	5.4
424-433	YTYRPGVNL	224	A0201	18	<5
			A24	N.A.	<5
			A26	20	N.A.
425-433	TYRPGVNL	225	A0201	14	<5
			A24	N.A.	200
			B0702	16	<5
			B2705	16	5
426-433	YYRPGVNL	226	B08	16	<5
426-435	YYRPGVNLSL	227	A0201	17	<5
			B0702	15	<5
427-435	YRPGVNLSL	228	A0201	17	<5
			B2705	26	2000
			B2709	21	N.A.
428-435	RPGVNLSL	229	B08	17	<5
			B5101	17	N.A.
428-437	RPGVNLSLSC	230	B0702	14	<5
430-438	GVNLSLSCH	231	A26	16	N.A.
			B2705	15	<5
431-440	VNLSLSCHAA	232	A0203	19	N.A.
432-440	NLSLSCHAA	233	A0201	16	<5

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†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 30.

Example 28: CEA 437-464Table 28Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
438-447	HAASNPPAQY	234	A1	15	<5
439-447	AASNPPAQY	235	A1	17	<5
			A3	17	<5
442-451	NPPAQYSWLI	236	B0702	17	8
443-451	PPAQYSWLI	237	B0702	17	<5
			B5101	21	40
444-451	PAQYSWLI	238	B5101	20	N.A.
449-458	WLIDGNIQQH	239	A0201	17	<5
			A26	17	N.A.
			A3	21	<5
450-458	LIDGNIQQH	240	A0201	16	<5
			A26	19	N.A.
			A3	17	<5
450-459	LIDGNIQQHT	241	A0201	16	<5
			A26	15	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 31.

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Example 29: CEA 581-607Table 29Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
581-590	RSDPVTLDVL	242	A0201	16	<5
			A1	19	7.5
			A26	15	N.A.
			A24	N.A.	9.6
582-590	SDPVTLDVL	243	A0201	16	<5
582-591	SDPVTLDVLY	244	A1	19	<5
583-590	DPVTLDVL	245	B08	16	<5
			B5101	25	N.A.
583-591	DPVTLDVLY	246	A1	17	<5
			A26	18	N.A.
			B5101	16	6
588-597	DVLYGPDTPI	247	A26	16	N.A.
589-597	VLYGPDTPI	248	A0201	25	56.754
			A3	17	6.75
			B5101	17	11.44
596-605	PIISPPDSSY	249	A1	15	<5
			A26	25	N.A.
			A3	22	<5
597-605	IISPPDSSY	250	A1	20	5
			A26	24	N.A.
			A3	24	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 32.

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Example 30: CEA 595-622Table 30Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
597-606	IISPPDSSYL	251	A0201	22	27.464
			A26	21	N.A.
			A3	16	<5
			B0702	14	<5
599-606	SPPDSSYL	252	B08	18	<5
			B5101	17	N.A.
600-608	PPDSSYLSG	253	A1	16	<5
600-609	PPDSSYLSGA	254	B0702	17	<5
602-611	DSSYLSGANL	255	A26	16	N.A.
603-611	SSYLSGANL	256	A0201	15	<5
			B2705	17	50
604-613	SYLSGANLNL	257	A0201	15	<5
			A24	N.A.	300
605-613	YLSGANLNL	258	A0201	25	98.267
			A26	19	N.A.
			A3	15	<5
			B0702	16	<5
			B08	17	<5
610-618	NLNLSCHSA	259	A0201	18	<5

- 5 †Scores are given from the two binding prediction programs referenced above (see example 3) See also figure 33.

Example 31: CEA 615-641Table 3110 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
620-629	NPSPQYSWRI	260	B0702	19	8
622-629	SPQYSWRI	261	B08	15	<5
			B5101	20	N.A.
627-635	WRINGIPQQ	262	B2705	19	20
628-636	RINGIPQQH	263	A3	22	<5
			B2705	16	<5
628-637	RINGIPQQHT	264	A0201	15	<5
631-639	GIPQQHTQV	265	A0201	19	9.563
632-639	IPQQHTQV	266	B5101	20	N.A.

- †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 34.

Example 32: CEA 643-677Table 32Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
644-653	KITPNNNGTY	267	A1	20	5
			A26	22	N.A.
			A3	25	<5
645-653	ITPNNNGTY	268	A1	22	<5
			A26	21	N.A.
			A3	14	<5
647-656	PNNNGTYACF	269	A26	15	N.A.
648-656	NNNGTYACF	270	A26	17	N.A.
650-657	NGTYACFV	271	B5101	15	N.A.
661-670	ATGRNNSIVK	272	A3	20	<5
662-670	TGRNNSIVK	273	A3	18	<5
664-672	RNNSIVKSI	274	B2709	15	N.A.
666-674	NSIVKSITV	275	A0201	16	<5

5 †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 35.

Example 33: GAGE-1 6-3210 Table 33Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
7-16	STYRPRPRRY	276	A1	23	<5
			A26	21	N/A
			A3	15	<5
8-16	TYRPRPRRY	277	A1	19	<5
			A3	15	<5
			A3	17	<5
10-18	RPRPRRYVE	278	B0702	16	N/A
			B08	20	<5
			B5101	15	N/A
16-23	YVEPPEMI	279	B5101	15	N/A
22-31	MIGPMRPEQF	280	A26	23	N/A
			A3	19	<5
23-31	IGPMRPEQF	281	B08	15	<5
24-31	GPMRPEQF	282	B5101	16	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 36.

Example 34: GAGE-1 105-131Table 345 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
105-114	KTPEEEMRSH	283	A26	18	N/A
106-115	TPEEEMRSHY	284	A1	26	11.25
107-115	PEEEMRSHY	285	A1	26	<5
110-119	EMRSHYVAQT	286	A0201	15	<5
113-121	SHYVAQTGI	287	B5101	15	<5
115-124	YVAQTGILWL	288	A0201	23	108.769
			A26	24	N/A
			A3	15	<5
116-124	VAQTGILWL	289	A0201	22	6.381
			B08	16	<5
			B2705	16	10
			B5101	20	78.65
116-125	VAQTGILWLL	290	A0201	19	8.701
117-125	AQTGILWLL	291	A0201	17	37.362
			B2705	16	200
118-126	QTGILWLLM	292	A26	19	N/A
118-127	QTGILWLLMN	293	A26	15	N/A
120-129	GILWLLMNNC	294	A26	15	N/A
121-129	ILWLLMNNC	295	A0201	15	161.227

† Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 37.

Example 35: GAGE-1 112-137Table 35Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
124-131	LLMNNCF	296	B08	16	<5
123-131	WLLMNNCF	297	A0201	22	1999.734
			A26	16	N/A
			B08	17	<5
122-130	LWLLMNNCF	298	B2705	15	<5
121-130	ILWLLMNNCF	299	A26	18	N/A
			A3	17	10
121-129	ILWLLMNNC	295	A0201	15	161.227
120-129	GILWLLMNNC	294	A26	15	N/A
118-127	QTGILWLLMN	293	A26	15	N/A
118-126	QTGILWLLM	292	A26	19	N/A
117-125	AQTGILWLL	291	A0201	17	37.362
			B2705	16	200
			B4402	17	N/A
116-125	VAQTGILWLL	290	A0201	19	8.701
116-124	VAQTGILWL	289	A0201	22	6.381
			B08	16	<5
			B2705	16	10
			B4402	15	N/A
			B5101	20	78.65
115-124	YVAQTGILWL	288	A0201	23	108.769
			A26	24	N/A
			A3	15	<5
113-121	SHYVAQTGI	287	B5101	15	<5

† Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 38.

Example 36 MAGE-1 51-77Table 36Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
62-70	SAFPTTINF	309	A26	15	N/A
			B4402	18	N/A
			B2705	17	25
61-70	ASAFPTTINF	310	B4402	15	N/A
60-68	GASAFPTTI	311	A0201	16	<5
			B5101	25	220
57-66	SPQGASAFPT	312	B0702	19	N/A

† Scores are given from the two binding prediction programs referenced above. See also figure 39.

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Example 37: Mage-1 126-153Table 37Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
144-151	FGKASESL	313	B08	21	<5
143-151	IFGKASESL	314	A26	16	N/A
			B2705	15	<5
142-151	EIFGKASESL	315	A0201	20	<5
			A26	29	N/A
			B4402	15	N/A
142-149	EIFGKASE	316	B08	16	<5
133-140	IKNYKHCF	317	B08	18	<5
132-140	VIKNYKHCF	318	A26	21	N/A
			B08	21	<5
131-140	SVIKNYKHCF	319	A26	23	N/A
			A3	18	<5
			B4402	15	N/A
132-139	VIKNYKHC	320	B08	15	<5
131-139	SVIKNYKHC	321	A26	18	N/A
128-136	MLESVIKNY	322	A1	28	45
			A26	24	N/A
			A3	17	<5
			B4402	15	N/A
127-136	EMLESVIKNY	323	A1	15	<5
			A26	23	N/A
			B4402	18	N/A
126-134	AEMLESVIK	324	A3	18	<5
			B2705	15	30
			B4402	16	N/A

† Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 40.

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Example 38: MAGE-2 272-299Table 385 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
274-283	GPRALIETSY	325	A1	15	<5
275-283	PRALIETSY	326	A1	15	<5
			B2705	23	100
276-284	RALIETSYV	327	A0201	18	19.658
			B5101	20	55
277-286	ALIETSYVKV	328	A0201	30	427.745
			A26	18	N/A
			A3	21	<5
278-286	LIETSYVKV	329	A0201	23	<5
			A26	17	N/A
			B5101	15	<5
278-287	LIETSYVKVL	330	A0201	22	<5
			A26	22	N/A
279-287	IETSYVKVL	331	A0201	15	<5
			B1510	15	N/A
			B5101	15	<5
280-289	ETSYVKVLH H	332	A26	21	N/A
282-291	SYVKVLHHT L	333	A0201	15	<5
283-291	YVKVLHHTL	334	A0201	19	<5
			A26	20	N/A
			A3	15	<5
			B08	21	<5
285-293	KVLHHTLKI	335	A0201	20	11.822
			A3	18	<5
			B5101	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3).] See also figure 41.

Example 39 MAGE-2 287-314Table 39Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
303-311	PLHERALRE	336	A3	19	<5
			B08	16	<5
302-309	PPLHERAL	337	B08	16	<5
			B5101	18	N/A
301-309	YPPLHERAL	338	B0702	21	N/A
			B08	18	<5
			B4402	15	N/A
			B5101	20	143
300-309	SYPPLHERAL	339	A0201	15	<5
			B4402	18	N/A
299-307	ISYPPLHER	340	B2705	17	25
298-307	HISYPPLHER	341	A26	15	N/A
292-299	KIGGEPHI	342	B5101	15	N/A
291-299	LKIGGEPHI	343	A0201	17	<5
290-299	TLKIGGEPHI	344	A0201	18	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 42.

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Example 40 Mage-3 287-314Table 40Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
303-311	PLHEWVLRE	345	A26	15	N/A
302-309	PPLHEWVL	346	B08	16	<5
			B5101	19	N/A
301-309	YPPLHEWVL	347	B0702	21	N/A
			B08	17	<5
			B5101	22	130
301-308	YPPLHEWV	348	B5101	22	N/A
300-308	SYPPLHEWV	349	A0201	15	<5
299-308	ISYPPLHEWV	350	A0201	15	6.656
298-307	HISYPPLHEW	351	A26	15	N/A
293-301	ISGGPHISY	352	A1	25	<5
292-301	KISGGPHISY	353	A1	20	<5
			A26	23	N/A
			A3	21	5.4

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 43.

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Example 41: Melan-A 44-71Table 415 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITH I	NIH
45-54	CWYCRRRNG Y	354	A1	16	<5
46-54	WYCRRRNGY	355	A1	16	<5
47-55	YCRRRNGYR	356	B08	15	<5
49-57	RRRNGYRAL	357	B08	17	<5
			B2705	26	1800
			B2709	24	N/A
51-60	RNGYRALMD K	358	A3	15	<5
52-60	NGYRALMDK	359	A3	18	<5
55-63	RALMDKSLH	360	B2705	16	<5
56-63	ALMDKSLH	361	B08	16	<5
55-64	RALMDKSLH V	362	A0201	17	<5
56-64	ALMDKSLHV	363	A0201	26	1055.104
			A3	18	<5
			B08	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 44.

Example 42: PRAME 274-301Table 42Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITH I	NIH
275-284	YISPEKEEQY	364	A1	21	5
			A26	23	N/A
			A3	20	<5
			B4402	15	N/A
276-284	ISPEKEEQY	365	A1	19	<5
			A26	15	N/A
277-285	SPEKEEQYI	366	B0702	17	N/A
			B5101	21	484
278-285	PEKEEQYI	367	B08	18	<5
279-288	EKKEEQYIAQF	368	A26	24	N/A
			B4402	16	N/A
280-288	KEEQYIAQF	369	A26	17	N/A
			B2705	19	45
			B4402	25	N/A
283-292	QYIAQFTSQF	370	A3	17	<5
			B4402	15	N/A
284-292	YIAQFTSQF	371	A0201	15	<5
			A26	24	N/A
			A3	19	<5
284-293	YIAQFTSQFL	372	A0201	22	74.314
			A26	21	N/A
285-293	IAQFTSQFL	373	A0201	15	<5
			B08	15	<5
			B5101	19	78.65
286-295	AQFTSQFLSL	374	A0201	16	15.226
			A26	15	N/A
			B0702	15	N/A
			A4402	18	N/A
287-295	QFTSQFLSL	375	A26	21	N/A
290-298	SQFLSLQCL	376	A0201	17	18.432
			A26	16	N/A
			B2705	16	1000
			B4402	15	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 45.

Example 43: PRAME 434-463Table 43Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
439-448	VLYPVPLESY	377	A0201	20	<5
			A1	21	5
			A26	25	N/A
			A3	25	67.5
440-448	LYPVPLESY	378	A1	16	<5
446-455	ESYEDIHGTL	379	A26	16	N/A
448-457	YEDIHGTLHL	380	A1	18	<5
449-457	EDIHGTLHL	381	B2705	15	<5
451-460	IHGTLHLERL	382	A0201	16	<5

5 †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 46.

Example 44: PRAME 452-480Table 44Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITH I	NIH
454-463	TLHLERLAYL	383	A0201	26	270.234
			A26	21	N/A
455-463	LHLERLAYL	384	A0201	22	<5
			B08	20	<5
			B1510	21	N/A
			B2705	15	<5
456-463	HLERLAYL	385	B08	17	<5
456-465	HLERLAYLH A	386	A3	16	<5
			A1	17	<5
458-467	ERLAYLHARL	387	A26	16	N/A
459-467	RLAYLHARL	388	A0201	24	21.362
			B08	17	<5
			B2705	18	90
			B2709	15	N/A
459-468	RLAYLHARL R	389	A3	22	<5
460-467	LAYLHARL	390	B08	15	<5
			B5101	20	N/A
460-468	LAYLHARLR	391	B5101	18	<5
461-470	AYLHARLREL	392	A0201	20	<5
			B4402	16	N/A
462-470	YLHARLREL	393	A0201	28	45.203
			B08	25	8
462-471	YLHARLRELL	394	A0201	22	48.151
			A26	16	N/A
463-471	LHARLRELL	395	A0201	15	<5
			B1510	22	N/A
464-471	HARLRELL	396	B08	30	320
			B5101	17	N/A
464-472	HARLRELLC	397	B08	20	16
469-478	ELLCELGRPS	398	A3	15	<5
470-478	LLCELGRPS	399	A0201	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 47.

Example 45: PSA 143-169Table 45Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
144-153	QEPALGTTCY	400	A1	15	<5
145-153	EPALGTTCY	401	A1	17	<5
			A26	17	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 48.

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Example 46: PSA 156-1883Table 46Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
162-171	PEEFLTPKKL	402	B4402	24	N.A.
163-171	EEFLTPKKL	403	A26	17	N.A.
			B4402	29	N.A.
165-173	FLTPKKLQC	404	A3	20	<5
			B08	17	<5
165-174	FLTPKKLQCV	405	A0201	26	735.86
			A26	15	N.A.
166-174	LTPKKLQCV	406	A0201	21	<5
			A26	18	N.A.
167-174	TPKKLQCV	407	B08	16	<5
			B5101	22	N.A.
167-175	TPKKLQCVD	408	B5101	15	<5
170-179	KLQCVDLHVI	409	A0201	24	34.433
			A3	17	<5
171-179	LQCVDLHVI	410	A0201	15	<5
			B5101	16	6.292

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 49.

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Example 47: PSCA 67-94

Table 47

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
73-81	DSQDYYVGK	411	A3	15	<5
74-82	SQDYYVGKK	412	A1	16	<5
74-83	SQDYYVGKK N	413	A1	15	<5
76-84	DYYVGKKNI	414	B5101	19	23.426
77-84	YYVGKKNI	415	B08	16	<5
78-86	YVGKKNITC	416	A3	15	<5
78-87	YVGKKNITCC	417	A26	15	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 50.

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Example 48: PSMA 378-405

Table 48

10 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
381-390	WVFGGIDPQS	418	A26	16	N/A
			A3	15	<5
385-394	GIDPQSGAAV	419	A0201	24	<5
			A0203	17	N/A
			A1	15	10
			A26	15	N/A
			A3	18	<5
386-394	IDPQSGAAV	420	A0201	15	<5
387-394	DPQSGAAV	421	B5101	22	N/A
387-395	DPQSGAAVV	422	B0702	18	N/A
			B5101	26	440
387-396	DPQSGAAVVH	423	A3	15	<5
388-396	PQSGAAVVH	424	A3	17	<5
389-398	QSGAAVVHEI	425	A0201	15	<5
390-398	SGAAVVHEI	426	A0201	19	<5
			B5101	21	88
391-398	GAAVVHEI	427	B5101	23	N/A
391-399	GAAVVHEIV	428	A0201	17	<5
			B5101	20	133.1
392-399	AAVVHEIV	429	B5101	19	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 51.

Example 49: PSMA 597-623Table 49Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
597-605	CRDYAVVLR	430	B2705	22	N/A
598-607	RDYAVVLRK Y	431	A1	17	<5
			A26	15	N/A
			A3	16	<5
599-607	DYAVVLRKY	432	A1	19	<5
			A26	22	N/A
600-607	YAVVLRKY	433	B5101	17	N/A
602-611	VVLRKYADKI	434	A0201	17	<5
			A3	18	<5
603-611	VLRKYADKI	435	A0201	22	<5
			A3	16	<5
			B08	19	<5
			B5101	16	5.72
603-612	VLRKYADKIY	436	A1	17	<5
			A26	19	N/A
			A3	19	<5
604-611	LRKYADKI	437	B08	17	<5
604-612	LRKYADKIY	438	A1	15	<5
			B2705	19	N/A
605-614	RKYADKIYSI	439	A0201	16	<5
606-614	KYADKIYSI	440	A0201	20	<5
			B08	17	<5
607-614	YADKIYSI	441	B5101	27	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 52.

Example 50: PSMA 615-642Table 50Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
616-625	MKHPQEMKT Y	442	A1	19	<5
			A26	16	N/A
617-625	KHPQEMKTY	443	A1	15	<5
			A26	16	N/A
618-627	HPQEMKTYSV	444	A0201	15	<5
			B0702	17	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 53.

Example 51: SCP-1 57-86Table 51Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
62-71	IDSDPALQKV	445	A0201	19	<5
63-71	DSDPALQKV	446	A0201	17	<5
			A1	20	7.5
			A26	15	N/A
			B5101	15	5.324
67-76	ALQKVNFLPV	447	A0201	23	132.149
70-78	KVNFLPVLE	448	A3	16	<5
71-80	VNFLPVLEQV	449	A3	18	<5
72-80	NFLPVLEQV	450	A0201	16	<5
75-84	PVLEQVGNSD	451	A0201	18	<5
76-84	VLEQVGNSD	452	A3	18	<5
			A1	15	<5
			A3	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 54.

5

Example 52: SCP-1 201-227Table 52Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
202-210	YEREETRQV	453	A0201	16	<5
202-211	YEREETRQVY	454	A1	19	<5
			A3	15	<5
			A4402	22	N/A
203-211	EREETRQVY	455	A1	27	<5
			A26	19	N/A
			B2705	20	N/A
203-212	EREETRQVYM	456	A26	17	N/A
204-212	REETRQVYM	457	B2705	15	N/A
211-220	YMDLNSNIEK	458	A1	17	25
213-221	DLNSNIEKM	459	A0201	20	<5
			A26	28	N/A
216-226	SNIEKMITAF	460	A26	19	N/A
			B4402	19	N/A
217-225	NIEKMITAF	461	A26	26	N/A
			B2705	17	N/A
			B4402	16	N/A
218-225	IEKMITAF	462	B08	17	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 55.

10

Example 53: SCP-1 395-424Table 53Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
397-406	RLENYEDQLI	463	A0201	17	<5
			A3	15	<5
398-406	LENYEDQLI	464	B4402	19	N/A
398-407	LENYEDQLII	465	B4402	19	N/A
399-407	ENYEDQLII	466	B5101	17	19.36
399-408	ENYEDQLIIL	467	A26	20	N/A
400-408	NYEDQLIIL	468	A1	16	<5
400-409	NYEDQLIILT	469	A1	16	<5
401-409	YEDQLIILT	470	A1	18	<5
			B4402	16	N/A
401-410	YEDQLIILTM	471	A1	18	<5
			B4402	16	N/A
402-410	EDQLIILTM	472	A26	18	N/A
			B2705	15	<5
406-415	IILTMELQKT	473	A0201	22	14.824
407-415	ILTMELQKT	474	A26	16	N/A
			A0201	21	29.137

†Scores are given from the two binding prediction programs referenced above (see example 3).. See also figure 56.

5

Example 54: SCP-1 416-442Table 54Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
424-432	KLTNNKEVE	475	A3	18	<5
424-433	KLTNNKEVEL	476	A0201	24	74.768
			A26	18	N/A
			A3	18	<5
425-433	LTNNKEVEL	477	A0201	22	<5
			A26	21	N/A
			B08	22	<5
429-438	KEVELEELKK	478	A3	17	<5
430-438	EVELEELKK	479	A1	18	90
			A26	17	N/A
			A3	24	<5
			B2705	15	<5
430-439	EVELEELKKV	480	A0201	15	<5
			A26	21	N/A
431-439	VELEELKKV	481	A0201	20	80.217
			A4402	15	N/A
			B5101	17	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 57.

10

Example 55: SCP-1 518-545Table 55Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
530-539	ETSDMTLELK	482	A26	21	N/A
531-539	TSDMTLELK	483	A1	16	15

5 †Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 58.

Example 56: SCP-1 545-578Table 5610 Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
548-556	NKKQEERML	484	B08	20	<5
553-562	ERMLTQIENL	485	A26	19	N/A
			B4402	17	N/A
554-562	RMLTQIENL	486	A0201	24	64.335
			B2705	21	150
			B2709	17	N/A
			B4402	15	N/A
555-562	MLTQIENL	487	B08	16	<5
555-564	MLTQIENLQE	488	A3	16	<5
560-569	ENLQETETQL	489	A26	16	N/A
561-569	NLQETETQL	490	A0201	22	87.586
			A26	19	N/A
			A3	15	<5
			B08	18	<5
561-570	NLQETETQLR	491	A3	15	6

†Scores are given from the two binding prediction programs referenced above (see example 3).. See also figure 59.

Example 57: SCP-1 559-585Table 57Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
567-576	TQLRNELEYV	492	A0201	16	161.729
568-576	QLRNELEYV	493	A0201	24	32.765
			A3	16	<5
571-580	NELEYVREEL	494	A0201	16	<5
			B4402	23	N/A
572-580	ELEYVREEL	495	A0201	17	<5
			A26	23	N/A
			B08	20	<5
573-580	LEYVREEL	496	B08	19	<5
574-583	EYVREELKQK	497	A3	16	<5
575-583	YVREELKQK	498	A26	17	N/A
			A3	27	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 60.

5

Example 58: SCP-1 665-701Table 58Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
675-684	LEEVEKAKV	499	A0201	27	31.026
676-684	LEEVEKAKV	500	A0201	15	<5
676-685	LEEVEKAKVI	501	A4402	22	N/A
677-685	EEVEKAKVI	502	B08	21	<5
			B4402	24	N/A
			B5101	18	<5
681-690	KAKVIADEAV	503	A0201	15	<5
683-692	KVIADAEAVKL	504	A0201	21	6.542
			A26	22	N/A
			A3	25	<5
			B4402	17	N/A
684-692	VIADEAVKL	505	A0201	26	20.473
			A26	22	N/A
			A3	17	<5
			B08	16	<5
			B2705	15	N/A
685-692	IADEAVKL	506	B08	17	<5
			B5101	21	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 61.

10

Example 59: SCP-1 694-7205 Table 59Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
694-702	KEIDKRCQH	507	A3	16	<5
			A4402	17	N/A
694-703	KEIDKRCQH K	508	A3	17	<5
			B4402	15	N/A
695-703	EIDKRCQHK	509	A26	20	N/A
			A3	20	<5
695-704	EIDKRCQHKI	510	A0201	16	<5
			A26	19	N/A
696-704	IDKRCQHKI	511	B08	17	<5
697-704	DKRCQHKI	512	B5101	16	N/A
698-706	KRCQHKIAE	513	B2705	16	60
698-707	KRCQHKIAE M	514	A26	15	N/A
			A26	15	N/A
699-707	RCQHKIAEM	515	B2705	18	9
			A26	15	N/A
701-710	QHKIAEMVA L	516	A26	15	N/A
702-710	HKIAEMVAL	517	A0201	15	<5
			A26	16	N/A
			B4402	16	N/A
703-710	KIAEMVAL	518	B08	16	<5

†Scores are given from the two binding prediction programs referenced

[0386] above (see example 3)

10 [0387] See also figure 62.

Example 60: SCP-1 735-769Table 60Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
737-746	QEQSSLRASL	519	B4402	21	N.A.
738-746	EQSSLRASL	520	A26	22	N.A.
			B0702	15	6
739-746	QSSLRASL	521	B08	19	<5
741-750	SLRASLEIEL	522	A0201	24	<5
			A26	17	N.A.
			A3	16	<5
742-750	LRASLEIEL	523	A0201	17	<5
			B2705	23	2000
			B2709	21	N.A.
743-750	RASLEIEL	524	B5101	17	N.A.
744-753	ASLEIELSNL	525	A0201	20	<5
			A26	16	N.A.
745-753	SLEIELSNL	526	A0201	25	<5
			A26	22	N.A.
			A3	15	<5
			B08	18	<5
745-754	SLEIELSNLK	527	A1	15	18
			A3	22	20
746-754	LEIELSNLK	528	B2705	16	30
			B4402	15	N.A.
747-755	EIELSNLKA	529	A1	19	<5
			A26	18	N.A.
749-758	ELSNLKAELL	530	A0201	17	<5
			A26	22	N.A.
750-758	LSNLKAELL	531	B08	21	<5
751-760	SNLKAELLSV	532	A0201	21	<5
752-760	NLKAELLSV	533	A0201	26	5.599
			A3	18	<5
			B08	16	<5
752-761	NLKAELLSV K	534	A3	30	30
753-761	LKAELLSVK	535	A3	19	<5
753-762	LKAELLSVK K	536	A3	16	<5
754-762	KAELLSVKK	537	A3	18	<5
			B2705	18	30
755-763	AELLSVKKQ	538	B4402	19	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 63.

Example 61: SCP-1 786-8165 Table 61Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
787-796	EKDKKKTQTF	539	A26	19	N/A
			B4402	15	N/A
788-796	KKDKKKTQTF	540	B08	16	<5
			B2705	16	<5
789-796	KDKKKTQTF	541	B08	16	<5
797-806	LLETPDIYW K	542	A0201	16	<5
			A3	21	90
798-806	LETPDIYWK	543	B2705	15	30
			B4402	16	N/A
798-807	LETPDIYWK L	544	A0201	15	7.944
			A26	15	N/A
			A4402	24	N/A
799-807	ETPDIYWKL	545	A26	31	N/A
			B4402	16	N/A
800-807	TPDIYWKL	546	B08	16	<5
			B5101	19	N/A

†Scores are given from the two binding prediction programs referenced

[0390] above (see example 3)

10

[0391] See also figure 64.

Example 62: SCP-1 806-833Table 62Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
809-817	SKAVPSQTV	547	A0201	17	<5
810-817	KAVPSQTV	548	B5101	19	N/A
812-821	VPSQTVSRNF	549	B0702	18	N/A
815-824	QTVSRNFTSV	550	A0201	16	<5
			A26	16	N/A
816-824	TVSRNFTSV	551	A0201	16	11.426
			A26	15	N/A
			A3	16	<5
816-825	TVSRNFTSVD	552	A3	20	<5
823-832	SVDHGISKDK	553	A3	21	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 65.

5

Example 63: SCP-1 826-853Table 63Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
829-838	SKDKRDYLWT	554	A1	18	<5
832-840	KRDYLWTS	555	B2705	16	600
832-841	KRDYLWTS	556	A3	17	<5
833-841	RDYLWTS	557	A3	23	<5
			B2705	18	15
835-843	YLWTS	558	A0201	16	284.517
835-844	YLWTS	559	A0201	26	815.616
			A26	16	N/A
837-844	WTS	560	B08	20	<5
841-850	KNTLSTPLPK	561	A3	18	<5
842-850	NLSTPLPK	562	A3	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 66.

10

Example 64: SCP-1 832-859Table 64Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
832-840	KRDYLWTSA	563	B2705	16	600
832-841	KRDYLWTSAK	564	A3	17	<5
833-841	RDYLWTSAK	565	A3	23	<5
			B2705	18	15
835-843	YLWTSAKNT	566	A0201	16	284.517
839-846	SAKNTLST	567	B08	16	<5
841-850	KNTLSTPLPK	568	A3	18	<5
842-850	NTLSTPLPK	569	A3	16	<5
843-852	TLSTPLPKAY	570	A1	16	<5
			A26	19	N/A
			A3	18	<5
			B4402	17	N/A
844-852	LSTPLPKAY	571	A1	23	7.5
			A4402	18	N/A

† Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 67.

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Example 65: SSX-2 1-27Table 65Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
5-12	DAFARRPT	572	B5101	18	N/A
7-15	FARRPTVGA	573	A0201	15	<5
8-17	ARRPTVGAQI	574	A3	18	<5
9-17	RRPTVGAQI	575	B2705	23	1800
			B2709	23	N/A
10-17	RPTVGAQI	576	B5101	20	N/A
13-21	VGAQIPEKI	577	B5101	20	125.84
14-21	GAQIPEKI	578	B5101	25	N/A
15-24	AQIPEKIQKA	579	A0201	16	<5
16-24	QIPEKIQKA	580	A0201	21	6.442
			A26	20	N/A
			B08	17	<5
16-25	QIPEKIQKAF	581	A26	24	N/A
			A3	16	<5
17-24	IPEKIQKA	582	B5101	19	N/A
17-25	IPEKIQKAF	583	B0702	19	N/A
			B08	15	<5
			B2705	16	<5
18-25	PEKIQKAF	584	B08	16	<5

† Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 68.

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Example 66: Survivin 116-142Table 66Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
116-124	ETNNKKKEF	585	A26	28	N/A
			B08	20	<5
117-124	TNNKKKEF	586	B08	16	<5
122-131	KEFEETAKKV	587	A0201	15	71.806
123-131	EFEETAKKV	588	A26	15	N/A
			B5101	15	5.324
127-134	TAKKVRRA	589	B5101	17	N/A
126-134	ETAKKVRRA	590	A26	24	N/A
128-136	AKKVRRAIE	591	B08	19	<5
129-138	KKVRRAIEQL	592	A0201	15	<5
130-138	KVRRAIEQL	593	A0201	19	<5
			A26	23	N/A
			A3	22	<5
			B08	17	<5
			B2705	16	30
130-139	KVRRAIEQLA	594	A3	19	<5
131-138	VRRAIEQL	595	B08	17	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 69.

5

Example 67: BAGE 1-35Table 67Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
24-31	SPVVSRL	596	B08	19	<5
			B5101	17	N/A
21-29	KBESPVSW	597	B4402	23	N/A
19-27	LMKEESPVV	598	A0201	22	5.024
			B5101	15	<5
18-27	RLMKEESPVV	599	A0201	22	105.51
			A3	18	<5
18-26	RLMKEESPV	600	A0201	21	257.342
			A3	17	<5
14-22	LLQARLMKE	601	A0201	18	<5
			A3	15	<5
13-22	QLQARLMKE	602	A0201	18	<5
			A26	15	N/A
			A3	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 70.

10

Example 68Epitope Clusters.

Known and predicted epitopes are generally not evenly distributed across the sequences of protein antigens. As referred to above, we have defined segments of sequence containing a higher than average density of (known or predicted) epitopes as epitope clusters. Among the uses of epitope clusters is the incorporation of their sequence into substrate peptides used in proteasomal digestion analysis as described herein, or to otherwise inform the selection and design of such substrates. Epitope clusters can also be useful as vaccine components. Fuller discussions of the definition and uses of epitope clusters is found in PCT Publication No. WO 01/82963; PCT Publication No. WO 03/057823; and U.S. Patent Application No. 09/561,571 entitled EPITOPE CLUSTERS and in U.S. Patent Application No. 10/026,066 entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS." Epitopes and epitope clusters for many of the TAA mentioned herein have been previously disclosed in PCT Publication No. WO 02/081646; in Patent Application No. 09/561,571; in U.S. Patent Application No. 10/117,937; U.S. Provisional Application Nos. 60/337,017 filed on November 7, 2001, and 60/363,210 filed on March 7, 2002, all entitled EPITOPE SEQUENCES. The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

For the TuAAs survivin (SEQ ID NO. 98) and GAGE-1 (SEQ ID NO. 96) the following tables (68-73) present 9-mer epitopes predicted for HLA-A2 binding using both the SYFPEITHI and NIH algorithms and the epitope density of regions of overlapping epitopes, and of epitopes in the whole protein, and the ratio of these two densities. (The ratio must exceed one for there to be a cluster by the above definition; requiring higher values of this ratio reflect preferred embodiments). Individual 9-mers are ranked by score and identified by the position of their first amino in the complete protein sequence. Each potential cluster from a protein is numbered. The range of amino acid positions within the complete sequence that the cluster covers is indicated, as are the rankings of the individual predicted epitopes it is made up of.

Table 68**HLA-A2 Epitope cluster analysis for Survivin (NIH algorithm)**

Length of protein sequence: 142 amino acids

Number of 9-mers: 134

Number of 9-mers with NIH score = 5: 2

Cluster	AA	Peptide Rank	Start Position	Score	Peptides/AAs		Ratio
					Cluster	Whole Pro.	
1	13-28	1	13	10.26	0.125	0.014	8.875
SEQ ID NO:603		2	20	4.919			

30

Table 69

HLA-A2 Epitope cluster analysis for Survivin (SYFPEITHI algorithm)

Length of protein sequence: 142 amino acids

Number of 9-mers: 134

Number of 9-mers with SYFPEITHI score = 15: 10

Cluster	AA	Peptide	Start	Score	Peptides/AAs		Ratio
		Rank	Position		Cluster	Whole Pro.	
1	13-28	5	13	17	0.125	0.070	1.775
SEQ ID NO:603		4	20	18			
2	79-111	8	79	15	0.182	0.070	2.597
SEQ ID NO:604		9	81	15			
		6	88	17			
		1	96	23			
		7	97	16			
		10	103	15			
3	130-141	2	130	19	0.167	0.070	2.381
SEQ ID NO:605		3	133	19			

Table 70

HLA-A2 Epitope cluster analysis for GAGE-1 (NIH algorithm)

Length of protein sequence: 138 amino acids

Number of 9-mers: 130

Number of 9-mers with NIH score = 5: 5

Cluster	AA	Peptide	Start	Score	Peptides/AAs		Ratio
		Rank	Position		Cluster	Whole Pro.	
1	116-133	1	123	1999.734	0.278	0.036	7.667
SEQ ID NO:606		2	121	161.227			
		3	125	49.834			
		4	117	37.362			
		5	116	6.381			

5

Table 71

HLA-A2 Epitope cluster analysis for GAGE-1 (SYFPEITHI algorithm)

Length of protein sequence: 138 amino acids

Number of 9-mers: 130

Number of 9-mers with SYFPEITHI score = 5: 6

Cluster	AA	Peptide	Start	Score	Peptides/AAs		Ratio
		Rank	Position		Cluster	Whole Pro.	
1	116-133	1	116	22	0.333	0.043	7.667
SEQ ID NO:606		2	123	22			
		3	125	22			
		4	117	17			
		5	120	16			
		6	121	15			

Table 72**HLA-A2 Epitope cluster analysis for BAGE (NIH algorithm)**

Length of protein sequence: 43 amino acids

Number of 9-mers included: 35

Number of 9-mers with NIH score = 5: 4

Cluster	AA	Peptide	Start	Score	Peptides/AAs		Ratio
		Rank			Cluster	Whole Pro.	
1	7-17	2	7	98.267	0.182	0.093	1.955
SEQ ID NO:607		3	9	11.426			
2	18-27	1	18	257.342	0.200	0.093	2.151
SEQ ID NO:608		4	19	5.024			

5 Table 73**HLA-A2 Epitope cluster analysis for BAGE (SYFPEITHI algorithm)**

Length of protein sequence: 43 amino acids

Number of 9-mers included: 35

Number of 9-mers with SYFPEITHI score = 15: 10

Cluster	AA	Peptide	Start	Score	Peptides/AAs		Ratio
		Rank			Cluster	Whole Pro.	
1	2-27	6	2	18	0.308	0.233	1.323
SEQ ID NO:609		9	6	16			
		1	7	23			
		3	9	21			
		5	11	19			
		7	14	18			
		4	18	21			
		2	19	22			
2	30-39	8	30	17	0.200	0.233	0.858
SEQ ID NO:610		10	31	15			

[0406] The embodiments of the invention are applicable to and contemplate variations in the sequences of the target antigens provided herein, including those disclosed in the various databases that are accessible by the world wide web. Specifically for the specific sequences disclosed herein, variation in sequences can be found by using the provided accession numbers to access information for each antigen.

15 TYROSINASE PROTEIN; SEQ ID NO 2

1 MLLAVLYCLL WSFQTSAGHF PRACVSSKNL MEKECCPPWS GDRSPCGQLS
GRGSCQNILL
61 SNAPLGPQFP FTGVDDRESW PSVFYNRTCQ CSGNFMGFNC GNCKFGFWGP
NCTERRLLVR

121 RNIFDLSAPE KDKFFAYLTL AKHTISSDYV IPIGTYGQMK NGSTPMFNDI
 NIYDLFVWMH
 181 YYVSM DALLG GSEIWRDIDF AHEAPAFLPW HRLFLLRWEQ EIQLTG DEN
 FTIPYWDWRD
 5 241 AEKCDICTDE YMGGQHPTNP NLLSPASFFS SWQIVCSRLE EYNHQSLCN
 GTPEGPLRRN
 301 PGNHDKSRTP RLPSSADVEF CLSLTQYESG SMDKAANFSF RNTLEGFASP
 LTGIADASQS
 361 SMHNALHIYM NGTMSQVQGS ANDPIFLLHH AFVDSIFEQW LRRHRPLQEV
 10 YPEANAPIGH
 421 NRESYMPFI PLYRNGDFFI SSKDLGYDYS YLQSDPDSF QDYIKSYLEQ
 ASRIWSWLLG
 481 AAMVGAVLTA LLAGLVSLLC RHKRKQLPEE KQPLLMEKED YHSLYQSHL
 15 SSX-2 PROTEIN; SEQ ID NO 3
 1 MNGDDAFARR PTVGAQIPEK IQKAFDDIAK YFSKEEWEKM KASEKIFYVY
 MKRKYEAMTK
 61 LGFKATLPPF MCNKRAEDFQ GNDLDNDPNR GNQVERPQMT FGRLQGISPK
 20 IMPKKPAEEG
 121 NDSEEVPEAS GPQNDGKELC PPGKPTTSEK IHERSGPKRG EHAWTHRLRE
 RKQLVIYEEI
 181 SDPEEDDE
 25 PSMA PROTEIN; SEQ ID NO 4
 1 MWNLHETDS AVATARRPRW LCAGALVLAG GFFLLGFLFG WFIKSSNEAT
 NITPKHNMKA
 61 FLDELKAENI KKFLYNFTQI PHLAGTEQNF QLAKQIQSQW KEFGLDSVEL
 30 AHYDVL LSYN
 121 NKTHPNYISI INEDGNEIFN TSLFEPPPPG YENVSDIVPP FSAFSPQGMP
 EGD LVYVNYA
 181 RTEDFFKLER DMKINCSGKI VIARYGKVFR GNKVKNQAQLA GAKGVILYSD
 PADYFAPGVK
 35 241 SYPDGWNLP GGVQRG NILN LNGAGDPLTP GYPANEYAYR RGIAEAVGLP
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 301 DAQKLEKMG GSAPPDSSWR GSLKVPYNVG PGFTGNFSTQ KVKMHIHSTN
 EVTRIYNVIG
 361 TLRGAVEPDR YVILGGHRDS WVFGGIDPQS GAAVVHEIVR SFGTLKKEGW
 40 RPRRTILFAS
 421 WDAEEFGLLG STEWAEENSR LLQERGVAYI NADSSIEGNY TLRVDCTPLM
 YSLVHNLTK
 481 LKSPDEGFEG KSLYESWTKK SPSPEFSGMP RISKLGSGND FEVFFQRLGI
 ASGRARYTKN
 45 541 WETNKFSGYP LYHSVYETYE LVEKFYDPMF KYHLTVAQVR GGMVFELANS
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 601 AVVLRKYADK IYSISMKHPQ EMKTYSVSFD SLFSAVKNFT EIASKFESERL
 QDFDKSNPIV
 661 LMMNDQLMF LERAFIDPLG LPDRPFYRHV IYAPSSHNKY AGESFPGIYD
 50 ALFDIESKVD
 721 PSKAWGEVKR QIYVAAFTVQ AAAETLSEVA

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 5 NGSTPMFNDINIYDLFVWMHYVVSMDALLGGSEIWRDIDFAHEAPAFPLPWHRLFLLRW
 EQEIQKLTGDENFTIPYWDWRDAEKCDICTDEYMGQHPNPNLLSPASFFSSWQIVC
 10 SRLEEYNHQSLCNGTPEGPLRRNPGNHDKSRTPLRPSSADVEFCLSLTQYESGSMDB
 AANFSFRNTLEGFASPLTGIADASQSSMHNALHIYMNGTMSQVQGSANDPIFLLHHAF
 VDSIFEQWLRHRPLQEYYPEANAPIGHNRESYMPFIPLYRNGDFFISSKDLGYDYS
 15 YLQSDPDPSFQDYIKSYLEQASRIWSWLLGAAMVGAVLTALLAGLVSLLCRHKRKQLP
 EEKQPLLMEKEDYHSLYQSHL"

 SEQ ID NO 5
 20 ORIGIN
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 ttcctgcaga
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 tgtggagttt
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 35 421 agagagacga ctcttggtga gaagaaacat ctctgatttg agtgccccag
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 ggggatctga
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 ggcatagact
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 agtacatggg
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 aacctaatac
 1801 aaagtgtagc cttcttccaa ctcaggtaga acacacctgt ctttgtcttg
 ctgttttcac
 25 1861 tcagcccttt taacattttc ccctaagccc atatgtctaa ggaaaggatg
 ctatttggtg
 1921 atgaggaact gttatttgta tgtgaattaa agtgctctta tttt

30

Homo sapiens synovial sarcoma, X breakpoint 2 (SSX2), mRNA.

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VERSION NM_003147.1 GI:10337582

SEQ ID NO 3

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SEQ ID NO 6

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 ttgcaaggag

50

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 atattgcaa

 181 atacttctct aaggaagagt gggaaaagat gaaagcctcg gagaaaatct
 tctatgtgta

 241 tatgaagaga aagtatgagg ctatgactaa actagggtttc aaggccaccc
 tcccaccttt

55

 301 catgtgtaat aaacggggccg aagacttcca ggggaatgat ttggataatg
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cctctgagaa
5      541 gattcacgag agatctggac caaaaggagg ggaacatgcc tggaccacac
gactgctga
      601 gagaaaacag ctggtgattt atgaagagat cagcgaccct gaggaagatg
acgagtaact
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10 ctttcacgaa
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15 Homo sapiens folate hydrolase (prostate-specific membrane antigen)
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VERSION NM_004476.1 GI:4758397

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GNFSTQKVKMHIHSTNEVTRIYNVIGTLRGAVEPDRIYVILGGHRDSWVFGGIDPQSGA
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40 DPMFKYHLTVAQVRGGMVFELANSIVLPFDCRDYAVVLRKYADKIYSISMKHPQEMKT
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      121 gcgaattcca gcctgcaggg ctgataagcg aggcattagt gagattgaga
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 301 accgcgcgcc gccgcgctg gctgtgcgct ggggcgctgg tgctggcggg
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 10 tcagcttgca
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 2641 aaaaaaaaaa aaa

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Human melanocyte-specific (pmel 17) gene, exons 2-5, and complete cds.

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 VERSION U20093.1 GI:1142634
 SEQ ID NO 70

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 40 EVMGTTLAEMSTPEATGMTPAEVSIVVLSGTTAAQVTTTEWVETTARELPIPEPEGPDASSIMSTE
 SITGSLGPLLDGTATLRLVKROVPLDCVLYRGSFSVTLDIVQGIESAEILQAVPSGEGDAFELTV
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45 SEQ ID NO 80
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	acccagtggt					
35	1381	ctatctggct	gaagctgacc	tctcctacac	ctgggacttt	ggagacagta
	gtggaaccct					
	1441	gatctctcgg	gcacctgtgg	tactcatac	ttacctggag	cctggcccag
	tcactgcca					
	1501	ggtggtcctg	caggctgcc	ttcctctcac	ctcctgtggc	tcctccccag
40	ttccaggcac					
	1561	cacagatggg	cacaggccaa	ctgcagaggc	ccctaacc	acagctggcc
	aagtgcctac					
	1621	tacagaagtt	gtgggtacta	cacctgggtc	ggcgccaact	gcagagccct
	ctggaaccac					
45	1681	atctgtgcag	gtgccaaaca	ctgaagtc	aagcactgca	cctgtgcaga
	tgccaactgc					
	1741	agagagcaca	ggtatgacac	ctgagaagg	gccagtttca	gaggtcatgg
	gtaccacact					
	1801	ggcagagatg	tcaactccag	aggctacagg	tatgacacct	gcagaggtat
50	caattgtggt					
	1861	gctttctgga	accacagctg	cacaggtaac	aactacagag	tgggtggaga
	ccacagctag					
	1921	agagctacct	atccctgagc	ctgaagggtc	agatgccagc	tcaatcatgt
	ctacggaaa					
55	1981	tattacaggt	tcctggggcc	ccctgctgga	tgggtacagcc	accttaaggc
	tgggtgaagag					
	2041	acaagtcccc	ctggattgtg	ttctgtatcg	atatgggtcc	ttttccgtca
	ccctggacat					

```

      2101 tgtccagggt attgaaagt ccgagatcct gcaggctgtg ccgtccggtg
agggggatgc
      2161 atttgagctg actgtgtcct gccaaaggcg gctgccccag gaagcctgca
tgagagatctc
5      2221 atcgccaggg tgccagcccc ctgcccagcg gctgtgccag cctgtgctac
ccagcccagc
      2281 ctgccagctg gttctgcacc agatactgaa ggggtggctcg gggacatact
gcctcaatgt
      2341 gtctctggct gataccaaca gcctggcagt ggtcagcacc cagcttatca
10      tgcctggtag
      2401 gtccttgga cagagactaag tgaggaggga agtggataga ggggacagct
ggcaagcagc
      2461 agacatgagt gaagcagtgc ctgggattct tctcacaggt caagaagcag
gccttgggca
15      2521 gggtccgctg atcgtgggca tcttgctggg gttgatggct gtggtccttg
catctctgat
      2581 atataggcgc agacttatga agcaagactt ctccgtaccc cagttgccac
atagcagcag
      2641 tcaactggctg cgtctacccc gcactctctg ctcttgctcc attggtgaga
20      atagccccct
      2701 cctcagtggg cagcaggtct gagtactctc atatgatgct gtgattttcc
tgaggttgac
      2761 agaaacacct atatttcccc cagtcttccc tgggagacta ctattaactg
aaataaaa
25      //

```

Homo sapiens kallikrein 3, (prostate specific antigen) (KLK3), mRNA.

```

30      ACCESSION      NM_001648
      VERSION          NM_001648.1  GI:4502172
      SEQ ID NO 78

```

```

35      /translation="MWVPVFLTSLVWIGAAPLILSRIVGGWECEKHSQPWQVLVAS
RGRAVCGGVLVHPQWVLTAAHCIRNKSIVLLGRHSLFHPEDTGQVFQVSHSFPHPLYDMSLLKNRF
LRPGDDSSHDLMLLRLSEPAELTDAVKVMDLPTQEPALGTTTCYASGWGSIPEEFLLTPKKLQCVDL
HVISNDVCAQVHPQKVTKFMLCAGRWTGGKSTCSGDSGGPLVCNGVLQGITSWGSEPCALPERPSL
YTKVVHYRKWIKDTIVANP"

```

```

40      SEQ ID NO 86
      ORIGIN

```

```

      1 agccccaagc ttaccacctg caccoggaga gctgtgtgtc accatgtggg
tcccggttgt
      61 cttcctcacc ctgtccgtga cgtggattgg tgctgcaccc ctcatcctgt
45      ctcggattgt
      121 gggaggctgg gagtgcgaga agcattccca accctggcag gtgcttgtgg
cctctcgtgg
      181 cagggcagtc tgcggcgggtg ttctggtgca cccccagtgg gtccctcacag
ctgcccactg
50      241 catcaggaac aaaagcgtga tcttgctggg tcggcacagc ctgtttcatc
ctgaagacac
      301 aggccaggta tttcaggta gccacagctt cccacacccg ctctacgata
tgagcctcct
      361 gaagaatcga ttcctcaggc caggatgatga ctccagccac gacctcatgc
55      tgctccgcct
      421 gtcagagcct gccagactca cgatgctgtg gaaggtcatg gacctgcccc
cccaggagcc

```

```

      481 agcactgggg accacctgct acgcctcagg ctggggcagc attgaaccag
aggagttctt
      541 gaccccaaag aaacttcagt gtgtggacct ccatgttatt tccaatgacg
tgtgtgcgca
5      601 agttcaccct cagaaggtga ccaagttcat gctgtgtgct ggacgctgga
cagggggcaa
      661 aagcacctgc tcgggtgatt ctgggggccc acttgtctgt aatggtgtgc
ttcaaggtag
      721 cacgtcatgg ggcagtgaac catgtgccct gcccgaaagg ccttcctgt
10      acaccaaggt
      781 ggtgcattac cggaagtgga tcaaggacac catcgtggcc aaccctgag
cacccctatc
      841 aaccccctat tgtagtaaac ttggaacctt ggaaatgacc aggccaagac
tcaagcctcc
15      901 ccagttctac tgacctttgt ccttaggtgt gaggtccagg gttgctagga
aaagaaatca
      961 gcagacacag gtgtagacca gagtgtttct taaatggtgt aattttgtcc
tctctgtgtc
      1021 ctggggaata ctggccatgc ctggagacat atcactcaat ttctctgagg
20      acacagatag
      1081 gatggggtgt ctgtgttatt tgtggggtac agagatgaaa gaggggtggg
atccacactg
      1141 agagagtgga gagtgcacat tgctggacac tgtccatgaa gcactgagca
gaagctggag
25      1201 gcacaacgca ccagacactc acagcaagga tggagctgaa aacataaccc
actctgtcct
      1261 ggaggcactg ggaagcctag agaaggctgt gagccaagga gggagggtct
tcctttggca
      1321 tgggatgggg atgaagtaag gagagggact ggacccctg gaagctgatt
30      cactatgggg
      1381 ggaggtgtat tgaagtcctc cagacaaccc tcagatttga tgatttccta
gtagaactca
      1441 cagaaataaa gagctgttat actgtg
//

```

35

Human autoimmunogenic cancer/testis antigen NY-ESO-1 mRNA,
complete cds.

ACCESSION U87459

40 VERSION U87459.1 GI:1890098

SEQ ID NO 74

```

      /translation="MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAG
      ATGGRGPRGAGAARASGPGGGAPRGPHGGAASGLNGCCRCGARGPESRLLEF
45      YLAMPFATPMEAELARRSLAQDAPPLPVPGVLLKEFTVSGNILTIRLTAADH
      RQLQLSISSCLOQLSLMWITQCFLPVFLAQPPSGQRR"

```

SEQ ID NO 84

ORIGIN

```

50      1 atcctcgtgg gccctgacct tctctctgag agccgggagc aggtccgga
gccatgcagg
      61 ccgaaggccg gggcacaggg ggttcgacgg gcgatgctga tggcccagga
ggccctggca
      121 ttctgatgg cccagggggc aatgctggcg gccagagaga ggcgggtgcc
55      acgggcggca
      181 gaggtccccg gggcgaggg gcagcaaggg cctcggggcc gggaggaggg
gccccgcggg

```

```

      241 gtccgcatgg cggcgcggtt tcagggtga atggatgctg cagatgcggg
gccagggggc
      301 cggagagccg cctgcttgag ttctacctcg ccatgccttt cgcgacaccc
atggaagcag
5      361 agctggcccg caggagcctg gccaggatg cccaccgct tcccgtgcca
ggggtgcttc
      421 tgaaggagtt cactgtgtcc ggcaacatac tgactatccg actgactgct
gcagaccacc
      481 gccaaactgca gctctccatc agctcctgtc tccagcagct ttccctgttg
10 atgtggatca
      541 cgcagtgtct tctgcccgtg tttttggctc agcctccctc agggcagagg
cgctaagccc
      601 agcctggcgc cccttcctag gtcatgcctc ctcccctagg gaatggtccc
agcacgagtg
15      661 gccagttcat tgtgggggcc tgattgtttg tcgctggagg aggacggctt
acatgtttgt
      721 ttctgtagaa aataaaactg agctacgaaa aa
//

```

```

20 LAGE-1a protein [Homo sapiens].
   ACCESSION   CAA11116
   PID         g3255959
   VERSION     CAA11116.1  GI:3255959

```

```

25 SEQ ID NO 75
   ORIGIN
      1 mqaegrgtgg stgdadgpgg pgipdgpggn aggpgeagat ggrgprgaga
arasgprgga
      61 prgphggaas aqdgrcpcga rrpdsrllel hitmpfsspm eaelvrrils
30 rdaaplprpg
      121 avlkdftvsg nllfirltaa dhrqlqlsis sclqqlslm witqcflpvf
laqapsqrr
      181
//
35

```

```

   LAGE-1b protein [Homo sapiens].
   ACCESSION   CAA11117
   PID         g3255960
40  VERSION     CAA11117.1  GI:3255960

   SEQ ID NO 76
   ORIGIN
      1 mqaegrgtgg stgdadgpgg pgipdgpggn aggpgeagat ggrgprgaga
45 arasgprgga
      61 prgphggaas aqdgrcpcga rrpdsrllel hitmpfsspm eaelvrrils
rdaaplprpg
      121 avlkdftvsg nllfmsvwdq dregagrmrv vgwglgsasp egqkardlrt
pkhkvsegrp
50  181 gtpgpppppeg aqgdgcrava fnvmfsaphi
//

```

```

55 Human antigen (MAGE-1) gene, complete cds.
   ACCESSION   M77481
   VERSION     M77481.1  GI:416114
   SEQ ID NO 71

```

/translation="MSLEQRSLHCKPEEALAEQOEALGLVCVQAATSSSSPL
 VLGTL EEVPTAGSTDPPQSPQGASAFPTTINFTRQRQPSEGSSSREEEGPST
 SCILESLFRAVITKKVADLVGFLLLKYRAREPVTKAEMLESVIKNYKHCPE
 IFGKASESLQLVFGIDVKEADPTGHSYVLVTCIGLSYDGLLDGNQIMPKTGF
 LIIVLVMIAMEGGHAPEEEIWEELSVM EVDGREHSAYGEPRKLLTQDLVQE
 KYLEYRQVPDSDPARYEFLWGPRLAETS YVKVLEYVIKVSARVRRFFPSLR
 EAALREEEEGV"

5
 10 SEQ ID NO 81
 ORIGIN
 1 ggatccaggc cctgccagga aaaatataag ggccctgcgt gagaacagag
 ggggtcatcc
 61 actgcatgag agtggggatg tcacagagtc cagcccaccc tcctggtagc
 15 actgagaagc
 121 cagggctgtg cttgcggtct gcaccctgag ggcccgtgga ttctctctcc
 tggagctcca
 181 ggaaccaggc agtgaggcct tgggtctgaga cagtatcctc aggtcacaga
 gcagaggatg
 20 241 cacaggggtgt gccagcagtg aatgtttgcc ctgaatgcac accaagggcc
 ccacctgcc
 301 caggacacat aggactccac agagtctggc ctcacctccc tactgtcagt
 cctgtagaat
 361 cgacctctgc tggcgggctg taccctgagt accctctcac ttctccttc
 25 aggttttcag
 421 gggacaggcc aaccocagagg acaggattcc ctggaggcca cagaggagca
 ccaaggagaa
 481 gatctgtaag taggcctttg ttagagtctc caaggttcag ttctcagctg
 aggcctctca
 30 541 cacactccct ctctccccag gcctgtgggt cttcattgcc cagctcctgc
 ccacactcct
 601 gcctgctgcc ctgacgagag tcatcatgtc tcttgagcag aggagtctgc
 actgcaagcc
 661 tgaggaagcc cttgaggccc aacaagaggc cctgggcctg gtgtgtgtgc
 35 aggctgccac
 721 ctctctctcc tctctctctg tctggggcac cctggaggag gtgcccactg
 ctgggtcaac
 781 agatcctccc cagagtctc agggagcctc cgcctttccc actaccatca
 acttcactcg
 40 841 acagaggcaa cccagtgagg gttccagcag ccgtgaagag gaggggcca
 gcacctcttg
 901 tctcctggag tccttgttcc gagcagtaat cactaagaag gtggctgatt
 tggttggttt
 961 tctgctcctc aaatatcgag ccaggagacc agtcacaaag gcagaaatgc
 45 tggagagtgt
 1021 catcaaaaat tacaagcact gttttcctga gatcttcggc aaagcctctg
 agtccttgca
 1081 gctgggtcttt ggcattgacg tgaaggaagc agacccacc ggccactcct
 atgtccttgt
 50 1141 cacctgccta ggtctctcct atgatggcct gctgggtgat aatcagatca
 tgcccaagac
 1201 aggtctcctg ataattgtcc tggatcatgat tgcaatggag ggcggccatg
 ctcttgagga
 1261 ggaaatctgg gaggagctga gtgtgatgga ggtgtatgat gggagggagc
 55 acagtgccta
 1321 tggggagccc aggaagctgc tcacccaaga tttggtgcag gaaaagtacc
 tggagtaccg

```

      1381 gcaggtgccg gacagtgatc ccgcacgcta tgagttcctg tgggggtccaa
      gggccctcgc
      1441 tgaaaccagc tatgtgaaag tccttgagta tgtgatcaag gtcagtgcaa
      gagttcgctt
5      1501 tttcttccca tccctgcgtg aagcagcttt gagagaggag gaagagggag
      tctgagcatg
      1561 agttgcagcc aaggccagtg ggagggggac tgggccagtg caccttccag
      ggccgcgtcc
      1621 agcagcttcc cctgcctcgt gtgacatgag gccattcctt cactctgaag
10      agagcgggtca
      1681 gtgttctcag tagtaggttt ctgttctatt gggtgacttg gagatttata
      tttgttctct
      1741 tttggaattg ttcaaagtgt tttttttaag ggatggttga atgaacttca
      gcatccaagt
15      1801 ttatgaatga cagcagtcac acagttctgt gtatatagtt taagggttaag
      agtcttgtgt
      1861 tttattcaga ttgggaaatc cattctatct tgtgaattgg gataataaca
      gcagtggaat
20      1921 aagtacttag aaatgtgaaa aatgagcagt aaaatagatg agataaagaa
      ctaaagaaat
      1981 taagagatag tcaattcttg ccttatacct cagtctattc tgtaaaatct
      ttaaagatat
      2041 atgcatacct ggatttcctt ggcttctttg agaatgtaag agaaattaaa
      tctgaataaa
25      2101 gaattcttcc tgttctactg ctcttttctt ctccatgcac tgagcatctg
      ctttttgtaa
      2161 ggccctgggt tagtagtgga gatgctaagg taagccagac tcatacccac
      ccatagggtc
      2221 gtagagtcta ggagctgcag tcacgtaatc gaggtggcaa gatgtcctct
30      aaagatgtag
      2281 ggaaaagtga gagaggggtg aggggtgtgg gctccgggtg agagtgggtg
      agtgtcaatg
      2341 ccctgagctg gggcattttg ggctttggga aactgcagtt ccttctgggg
      gagctgattg
35      2401 taatgatctt ggggtggatcc
      //

```

Human MAGE-2 gene exons 1-4, complete cds.

```

40  ACCESSION   L18920
      VERSION   L18920.1  GI:436180
      SEQ ID NO 72

```

```

45  /translation="MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQQTASSSSTLVEVT
      LGEVPAADSPSPPHSPQGASSFSTTINYTLWRQSDEGSSNQEEEGPRMFDPLE
      SEFQAAISRKMVELVHFLLLKYRAREPVTKAEMLESVLRNCQDFFPVIFSKASEYLQLVFGIE
      VVEVVPISHLYILVTCLGLSYDGLLDGNQVMPKTGLLIIVLAI AIEGDCAPEEKIWEELSML
      EVFEGREDSVFHPRKLLMQDLVQENYLEYRQVPGSDPACYEFLWGPRALIETSYVKVLHHTL
      KIGGEPHISYPPLHERALREGEE"

```

```

50  SEQ ID NO 82
      ORIGIN

```

```

      1 attccttcat caaacagcca ggagtgagga agaggaccct cctgagtgag
      gactgaggat
      61 ccaccctcac cacatagtgg gaccacagaa tccagctcag cccctcttgt
55  cagccctggt
      121 acacaactggc aatgatctca ccccgagcac acccctcccc ccaatgccac
      ttcgggccga

```

	181	ctcagagtca	gagacttggg	ctgaggggag	cagacacaat	cggcagagga
		tggcgggtcca				
	241	ggctcagtct	ggcatccaag	tcaggacctt	gagggatgac	caaaggcccc
		tccccacccc				
5	301	aactcccccg	accccaccag	gatctacagc	ctcaggatcc	ccgtcccaat
		ccctaccctt				
	361	acaccaacac	catcttcatg	cttaccacca	ccccccatc	cagatcccca
		tccgggcaga				
	421	atccggttcc	acccttgccg	tgaaccagg	gaagtcacgg	gcccggatgt
10		gacgccactg				
	481	acttgacat	tggaggtcag	aggacagcga	gattctcgcc	ctgagcaacg
		gcctgacgtc				
	541	ggcggaggga	agcaggcgca	ggctccgtga	ggaggcaagg	taagacgccg
		agggaggact				
15	601	gaggcgggcc	tcaccccaga	cagagggccc	ccaataatcc	agcgctgcct
		ctgctgccgg				
	661	gcctggacca	ccctgcagg	gaagacttct	caggtcagt	cgccaccacc
		tcaccccgcc				
	721	acccccgcc	gctttaaccg	caggggaactc	tggcgtaaga	gctttgtgtg
20		accagggcag				
	781	ggctggttag	aagtgtcag	ggccagact	cagccaggaa	tcaaggtcag
		gacccaaga				
	841	ggggactgag	ggcaaccac	cccctaccct	cactaccaat	cccatcccc
		aacaccaacc				
25	901	ccacccccat	ccctcaaaca	ccaacccac	ccccaaacc	cattcccatc
		tcctcccca				
	961	ccaccatcct	ggcagaatcc	ggctttgcc	ctgcaatcaa	cccacggaag
		ctccgggaat				
	1021	ggcgccaag	cacgggatc	ctgacgttca	catgtacggc	taagggagg
30		aaggggttgg				
	1081	gtctcgtgag	tatggccttt	gggatgcaga	ggaagggccc	aggcctcctg
		gaagacagt				
	1141	gagtccttag	gggaccagc	atgccaggac	agggggccca	ctgtaccctt
		gtctcaaact				
35	1201	gagccacctt	ttcattcagc	cgagggaatc	ctagggatgc	agaccactt
		cagcagggg				
	1261	ttggggccca	gcctgcgagg	agtcaagggg	aggaagaaga	gggaggactg
		aggggacctt				
	1321	ggagtccaga	tcagtggcaa	ccttgggctg	ggggatcctg	ggcacagtgg
40		ccgaatgtgc				
	1381	cccggtctca	ttgcaccttc	agggtgacag	agagttgagg	gctgtgtgtt
		gagggctggg				
	1441	acttcaggtc	agcagagggg	ggaatcccag	gatctgccgg	acccaaggtg
		tgcccccttc				
45	1501	atgaggactg	gggatacccc	cggcccagaa	agaagggatg	ccacagagtc
		tggaagtccc				
	1561	ttgttcttag	ctctggggga	acctgatcag	ggatggccct	aagtgacaat
		ctcatttgta				
	1621	ccacaggcag	gaggttgggg	aaccctcagg	gagataaggt	gttggtgtaa
50		agaggagctg				
	1681	tctgtctcatt	tcaggggggtt	gggggttgag	aaagggcagt	ccctggcagg
		agtaaagatg				
	1741	agtaaccac	aggaggccat	cataacgttc	accctagaac	caaaggggtc
		agccctggac				
55	1801	aacgcacgtg	ggggtaacag	gatgtggccc	ctcctcactt	gtctttccag
		atctcagga				
	1861	gttgatgacc	ttgttttcag	aaggtgactc	aggtcaacac	aggggcccc
		tctggtcgac				

	1921	agatgcagtg	gttctaggat	ctgccaagca	tccaggtgga	gagcctgagg
		taggattgag				
	1981	ggtaccctg	ggccagaatg	cagcaagggg	gccccataga	aatctgccct
		gcccctgcgg				
5	2041	ttacttcaga	gaccctgggc	agggctgtca	gctgaagtcc	ctccattatc
		ctgggatctt				
	2101	tgatgtcagg	gaaggggagg	ccttggtctg	aaggggctgg	agtcaggtca
		gtagagggag				
	2161	ggtctcaggc	cctgccagga	gtggacgtga	ggaccaagcg	gactcgtcac
10		ccaggacacc				
	2221	tggactccaa	tgaatttgga	catctctcgt	tgtccttcgc	gggaggacct
		ggtcacgtat				
	2281	ggccagatgt	gggtcccctc	atatccttct	gtaccatata	agggatgtga
		gttcttgaca				
15	2341	tgagagattc	tcaagccagc	aaaaggggtg	gattaggccc	tacaaggaga
		aaggtgaggg				
	2401	ccctgagtga	gcacagaggg	gaccctccac	ccaagtagag	tggggacctc
		acggagtctg				
	2461	gccaaccctg	ctgagacttc	tgggaatccg	tggctgtgct	tgagttctgc
20		acactgaaag				
	2521	cccgtgcatt	cctctcccag	gaatcaggag	ctccaggaac	caggcagtga
		ggccttggtc				
	2581	tgagtcagtg	tcctcaggtc	acagagcaga	ggggacgcag	acagtgccaa
		caactgaagg				
25	2641	ttgcctggaa	tgacacccaa	gggccccacc	cgcccagaac	aaatgggact
		ccagagggcc				
	2701	tggcctcacc	ctccctattc	tcagtctctg	agcctgagca	tgtgctggcc
		ggctgtaccc				
	2761	tgaggtgccc	tcccacttcc	tccttcaggt	tctgaggggg	acaggctgac
30		aagtaggacc				
	2821	cgaggcactg	gaggagcatt	gaaggagaag	atctgtaagt	aagcctttgt
		cagagcctcc				
	2881	aaggttcagt	tcagttctca	cctaaggcct	cacacacgct	ccttctctcc
		ccaggcctgt				
35	2941	gggtcttcat	tgcccagctc	ctgcccgcac	tcctgcctgc	tgccctgacc
		agagtcatca				
	3001	tgctcttga	gcagaggagt	cagcactgca	agcctgaaga	aggccttgag
		gcccagaggag				
	3061	aggccctggg	cctggtgggt	gcgcaggctc	ctgctactga	ggagcagcag
40		accgcttctt				
	3121	cctcttctac	tctagtggaa	gttaccctgg	gggaggtgcc	tgctgccgac
		tcaccgagtc				
	3181	ctccccacag	tcctcagggg	gcctccagct	tctcgactac	catcaactac
		actctttgga				
45	3241	gacaatccga	tgagggctcc	agcaaccaag	aagaggaggg	gccaagaatg
		tttcccagcc				
	3301	tgaggtccga	gttccaagca	gcaatcagta	ggaagatggg	tgagttgggt
		cattttctgc				
	3361	tcctcaagta	tcgagccagg	gagccggtca	caaaggcaga	aatgctggag
50		agtgtcctca				
	3421	gaaattgccg	ggacttcttt	cccgtgatct	tcagcaaagc	ctccgagtac
		ttgcagctgg				
	3481	tctttggcat	cgaggtgggt	gaagtgggtc	ccatcagcca	cttgtagatc
		cttgtcacct				
55	3541	gcctgggcct	ctcctacgat	ggcctgctgg	gcgacaatca	ggtcagtccc
		aagacaggcc				
	3601	tcctgataat	cgctctggcc	ataatcgcaa	tagagggcga	ctgtgcccct
		gaggagaaaa				

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      3661 tctgggagga gctgagtatg ttggagggtgt ttgaggggag ggaggacagt
gtcttcgcac
      3721 atcccaggaa gctgctcatg caagatctgg tgcaggaaaa ctacctggag
taccggcagg
5      3781 tgcccggcag tgatcctgca tgctacgagt tcctgtgggg tccaagggcc
ctcattgaaa
      3841 ccagctatgt gaaagtcctg caccatacac taaagatcgg tggagaacct
cacatttcct
      3901 acccaccctt gcatgaacgg gctttgagag agggagaaga gtgagtctca
10 gcacatgttg
      3961 cagccagggc cagtgggagg gggctctgggc cagtgcacct tccagggccc
catccattag
      4021 cttccactgc ctcgtgtgat atgaggccca ttctgcctc tttgaagaga
gcagtcagca
15      4081 ttcttagcag tgagtttctg ttctgttgga tgactttgag atttatcttt
ctttcctggt
      4141 ggaattgttc aaatgttcct tttaacaaat ggttgatga acttcagcat
ccaagtttat
      4201 gaatgacagt agtcacacat agtgctgttt atatagttaa ggggtaagag
20 tcctgttttt
      4261 tattcagatt gggaaatcca ttccattttg tgagttgtca cataataaca
gcagtggaa
      4321 atgtatttgc ctatattgtg aacgaattag cagtaaaata catgatacaa
ggaactcaaa
25      4381 agatagttaa ttcttgcctt atacctcagt ctattatgta aaattaa
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30 agtagtgagg
//

```

Human MAGE-3 antigen (MAGE-3) gene, complete cds.

```

35  ACCESSION   U03735
    VERSION    U03735.1  GI:468825
    SEQ ID NO  73

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40  /translation="MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQEAASSSSTLVEVTLGE
    VPAAESPDPPQSPQGASSLPPTMNYPLWSQSYEDSSNQEEGPSTFPDLESEFQAALSRKVAELVH
    FLLKRYRAREPVTKAEMLGSVVGNWQYFFPVIFSKASSSLQLVFGIELMEVDPIGHLYIFATCLGL
    SYDGLLDGNQIMPKAGLLIIVLAI IAREGDCAPEEKIWEELSVLEVFEGREDSILGDPKKLLTQHF
    VQENYLEYRQVPGSDPACYEFLWGPRLVETS YVKVLHMHVKISGGPHISYPPLHEWVLRGEE"

```

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45  SEQ ID NO  83
    ORIGIN

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50  ggcgggtccag
     121  gctcagccag gcatcaactt caggaccctg agggatgacc gaaggccccg
cccaccacc
     181  cccaactccc ccgaccccac caggatctac agcctcagga ccccggtccc
aatccttacc
55     241  ccttgcccca tcaccatctt catgcttacc tccaccccca tccgatcccc
atccaggcag
     301  aatccagttc caccctgcc cggaaccag ggtagtaccg ttgccaggat
gtgacgccac

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	361	tgacttgccg	attggagggtc	agaagaccgc	gagattctcg	ccctgagcaa
		cgagcgacgg				
	421	cctgacgtcg	gcgaggaggaa	gccggcccag	gctcgggtgag	gaggcaaggt
		aagacgctga				
5	481	gggaggactg	aggcgggcct	cacctcagac	agagggcctc	aaataatcca
		gtgctgcctc				
	541	tgctgccggg	cctggggccac	cccgcagggg	aagacttcca	ggctgggtcg
		ccactacctc				
	601	accccgccga	cccccgcgc	tttagccacg	gggaactctg	gggacagagc
10		ttaatgtggc				
	661	cagggcaggg	ctgggttagaa	gaggtcaggg	cccacgtgt	ggcaggaatc
		aaggtcagga				
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		cgtcccccaa				
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	1021	cagcatgcc	ggacaggggg	cccactgtac	ccctgtctca	aaccgaggca
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25	1081	cggctacggg	aatcctaggg	atgcagaccc	acttcagcag	ggggttgggg
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30		gctcattgcg				
	1261	ccttcaggg	gaccagagag	ttgagggctg	tggtctgaag	agtgggactt
		caggtcagca				
	1321	gagggaggaa	tcccaggatc	tgagggccc	aaggtgtacc	cccaaggggc
		ccctatgtgg				
35	1381	tggacagatg	cagtggctct	aggatctgcc	aagcatccag	gtgaagagac
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	1441	ttgagggtag	ccctgggaca	gaatgcggac	tgggggcccc	ataaaaatct
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	1501	tgctgttacc	tcagagagcc	tgggcagggc	tgtcagctga	gtccctcca
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	1561	atcactgatg	tcaggggaagg	ggaagccttg	gtctgagggg	gctgcactca
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		ctcaccaggg				
45	1681	gtacatggac	ttcaataaat	ttggacatct	ctcgttgtcc	tttccgggag
		gacctgggaa				
	1741	tgtatggcca	gatgtgggtc	ccctcatgtt	tttctgtacc	atatcaggta
		tgtgagttct				
	1801	tgacatgaga	gattctcagg	ccagcagaag	ggagggatta	ggccctataa
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	1861	gagggccctg	agtgagcaca	gaggggatcc	tccaccccag	tagagtgggg
		acctcacaga				
	1921	gtctggccaa	ccctcctgac	agttctggga	atccgtggct	gcgtttgctg
		tctgcacatt				
55	1981	gggggcccgt	ggattcctct	cccaggaatc	aggagctcca	ggaacaaggg
		agtgaggact				
	2041	tggtctgagg	cagtgtcctc	aggtcacaga	gtagaggggg	ctcagatagt
		gccaacggtg				

	2101	aagggtttgcc	ttggattcaa	accaagggcc	ccacctgccc	cagaacacat
	ggactccaga					
	2161	gcgcttgcc	tcacctcaa	tactttcagt	cctgcagcct	cagcatgcgc
	tgcccgatg					
5	2221	tacctgagg	tgccctctca	cttcctcctt	caggttctga	ggggacaggc
	tgacctggag					
	2281	gaccagaggc	ccccggagga	gcactgaagg	agaagatctg	taagtaagcc
	tttgtttagag					
	2341	cctccaaggt	tccattcagt	actcagctga	ggtctctcac	atgctccctc
10	tctccccagg					
	2401	ccagtgggtc	tccattgccc	agctcctgcc	cacactcccc	cctgttgccc
	tgaccagagt					
	2461	catcatgcct	cttgagcaga	ggagtcagca	ctgcaagcct	gaagaaggcc
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	ccgagtcacc					
	2641	agatcctccc	cagagtcctc	agggagcctc	cagcctcccc	actaccatga
20	actaccctct					
	2701	ctggagccaa	tcctatgagg	actccagcaa	ccaagaagag	gaggggccaa
	gcaccttccc					
	2761	tgacctggag	tccgagttcc	aagcagcaact	cagtaggaag	gtggccgagt
	tggttcattt					
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	tggggagtg					
	2881	cgtcggaaat	tggcagtatt	tctttcctgt	gatcttcagc	aaagcttcca
	gttccttgca					
	2941	gctggtcttt	ggcatcgagc	tgatggaagt	ggaccccatc	ggccacttgt
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	3001	cacctgcctg	ggcctctcct	acgatggcct	gctgggtgac	aatcagatca
	tgcccaaggc					
	3061	aggcctcctg	ataatcgtcc	tggccataat	cgcaagagag	ggcgactgtg
	ccccagga					
35	3121	gaaaatctgg	gaggagctga	gtgtgttaga	ggtgtttgag	gggagggaag
	acagtatctt					
	3181	gggggatccc	aagaagctgc	tcacccaaca	tttcgtgcag	gaaaactacc
	tggagtaccg					
	3241	gcagggtcccc	ggcagtgatc	ctgcatgtta	tgaattcctg	tgggggtccaa
40	gggcccctcgt					
	3301	tgaaaccagc	tatgtgaaag	tcctgcacca	tatggtaaag	atcagtggag
	gacctcacat					
	3361	ttcctaccca	cccctgcatg	agtgggtttt	gagagagggg	gaagagtgag
	tctgagcacg					
45	3421	agttgcagcc	agggccagtg	ggaggggggtc	tgggccagtg	caccttccgg
	ggccgcaccc					
	3481	cttagtttcc	actgcctcct	gtgacgtgag	gcccattctt	cactctttga
	agcgagcagt					
	3541	cagcattctt	agtagtgggt	ttctgttctg	ttggatgact	ttgagattat
50	tctttgtttc					
	3601	ctgttgagg	tgttcaaagt	ttccttttaa	cggatgggtg	aatgagcgtc
	agcatccagg					
	3661	tttatgaatg	acagtagtca	cacatagtgc	tgtttatata	gtttaggagt
	aagagtcttg					
55	3721	ttttttactc	aaattgggaa	atccattcca	ttttgtgaat	tgtgacataa
	taatagcagt					
	3781	ggtaaaagta	tttgcttaaa	attgtgagcg	aattagcaat	aacatacatg
	agataactca					

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      3841 agaaatcaaa agatagttga ttcttgccctt gtacctcaat ctattctgta
aaattaaaca
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taccatagg
      4081 gctgtagagc ctaggacctg cagtcataata attaaggtgg tgagaagtcc
10 tgtaagatgt
      4141 agaggaaatg taagagaggg gtgaggggtg ggcgctccgg gtgagagtag
tggaagtgtca
      4201 gtgc
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15 Homo sapiens prostate stem cell antigen (PSCA) mRNA, complete
   cds.
   ACCESSION   AF043498
   VERSION     AF043498.1   GI:2909843
20 SEQ ID NO 79

   /translation="MKAVLLALLMAGLALQPGTALLCYSCKAQVSNEDCLQVENCTQLGEQCW
TARIRAVGLLTVISKGCSLNCVDDSDQYYVGKKNITCCDTDLCNASGAHALQPAAAILALLPA
LGLLLWGPGQL"
25 SEQ ID NO 87
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      1 agggagaggc agtgaccatg aaggctgtgc tgcttgccct gttgatggca
ggcttgggccc
30      61 tgcagccagg cactgccctg ctgtgctact cctgcaaagc ccagggtgagc
aacgaggact
      121 gcctgcaggt ggagaactgc acccagctgg gggagcagtg ctggaccgcg
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gccacactg
      421 ggtgtggtgc cccaggcctt tgtgccactc ctcacagaac ctggcccagt
gggagcctgt
      481 cctggttcct gaggcacatc ctaacgcaag tttgaccatg tatgtttgca
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      541 ccnaaccctg accttcccat gggccttttc caggattccn accnggcaga
tcagttttag
      601 tganacanat ccgntgcag atggccctc caaccnttn tgttgntggt
tccatggccc
50      661 agcattttcc acccttaacc ctgtgttcag gcacttnttc ccccaggaag
ccttccctgc
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ccagcagggg
      781 acaggcaatc aggagggccc agtaaaggct gagatgaagt ggactgagta
55 gaactggagg
      841 acaagagttg acgtgagttc ctgggagttt ccagagatgg ggcctggagg
cctggaggaa

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901 ggggccaggc ctcacatttg tggggntccc gaatggcagc ctgagcacag
 cgtaggcct
 961 taataaacac ctgttgata agccaaaaaa
 //

5

GLANDULAR KALLIKREIN 1 PRECURSOR (TISSUE KALLIKREIN)
 (KIDNEY/PANCREAS/SALIVARY GLAND KALLIKREIN).

10 ACCESSION P06870
 PID g125170
 VERSION P06870 GI:125170

SEQ ID NO 105

ORIGIN

15 1 mwflvlclal slggtgaapp iqsriaggwe ceqhsqpwa alyhfstfqc
 ggilvhrqvw
 61 ltaahcisdn yqlwlgrhnl fddentaqfv hvsesfphpg fnmsllenht
 rqadedyshd
 121 lmlrltepa dtitdaskvv elptqepvg stclasgwgs iepenfsfpd
 20 dlqcvdlkil
 181 pndecekahv qkvtdfmlcv ghleggkdtc vgdsggplmc dgvlqgvtsv
 gyvpcgtpnk
 241 psvavrvlsy vkwiedtiaa ns
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25

ELASTASE 2A PRECURSOR.

30 ACCESSION P08217
 PID g119255
 VERSION P08217 GI:119255

SEQ ID NO 106

ORIGIN

35 1 mirtllllstl vagalscgdp typpvtrvv ggeearpnsw pwqvslyqys
 ngkwyhtcgg
 61 slianswvlt aahciissrt yrvlggrhnl yvaesgslav svskivvhkd
 wnsnqiskgn
 121 diallklanp vsldtkiqla clppagtilp nnypcyvtgw grlqtngavp
 dvlqggrllv
 40 181 vdyatcssa wwgssvktm icaggdgvis scngdsggpl ncqasdgwrw
 vhgivsfgr
 241 lgcnyyhkps vftrvsnyid winsviann
 //

45 pancreatic elastase IIB [Homo sapiens].

ACCESSION NP_056933
 PID g7705648
 VERSION NP_056933.1 GI:7705648

50 SEQ ID NO 107

ORIGIN

1 mirtllllstl vagalscgvs tyapdmrml ggeearpnsw pwqvslyqys
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 61 slianswvlt aahciissri yrvmlgqhn1 yvaesgslav svskivvhkd
 55 wnsnqvskgn
 121 diallklanp vsldtkiqla clppagtilp nnypcyvtgw grlqtngalp
 ddlkqgrllv

181 vdyatcsssg wwgstvktnm icaggdgvic tcngdsggpl ncqasdgrwe
 vhgigsltsv
 241 lgcnyyykps iftrvsnynd winsviann
 //

5

PRAME Homo sapiens preferentially expressed antigen in melanoma
 (PRAME), mRNA.

ACCESSION NM_006115

10 VERSION NM_006115.1 GI:5174640

SEQ ID NO 77

/translation="MERRRLWGSIQSRYISMSVWTSPRRLVELAGQSLLKDEALAIAALELLPREL
 FPPLFMAAFDGRHSQTLKAMVQAWPFTCLPLGVLMMKGQHLHLETFKAVLDGLDVLLAQEVRPRRWK
 15 LQVLDLRKNSHQDFWTVWSGNRASLYSFPEPEAAQPMTKKRKVDGLSTEAEQPFIPVEVLVDLFLK
 EGACDELFSYLIKVKRKNVLRCCCKLKI FAMPMDIKMILKMVQLDSIEDLEVTCTWKLP TLA
 KFSPYLGQMINLRRLLSHIHASSYISPEKEEQYIAQFTSQFLSLQCLQALYVDSLFFLRGRDLQD
 LRHVMNPLETSLITNCRLESGDVMHLSQSPSVSLSVLSLSGVMLTDVSPPEPLQALLERASATLQD
 LVFDECGITDDQLLALLPSLSHCSQLTTL SFYGNSSISALQSLLOHLIGLSNLTHVLYPVPLESY
 20 EDIHGTLHLERLAYLHARLRELLCELGRPSMVWLSANPCPHCGDRTFYDPEPILCPCFMPN"

SEQ ID NO 85

ORIGIN

1 gcttcagggt acagctcccc cgcagccaga agccgggcct gcagcccctc
 25 agcaccgctc
 61 cgggacaccc caccogcttc ccaggcgtga cctgtcaaca gcaacttcgc
 ggtgtggtga
 121 actctctgag gaaaaacat tttgattatt actctcagac gtgcgtggca
 acaagtgact
 30 181 gagacctaga aatccaagcg ttggagggtcc tgaggccagc ctaagtcgct
 tcaaaatgga
 241 acgaaggcgt ttgtgggggt ccattcagag ccgatacatc agcatgagtg
 tgtggacaag
 301 ccacaggaga cttgtggagc tggcagggca gagcctgctg aaggatgagg
 35 ccctggccat
 361 tgccgccctg gagttgctgc ccaggagct cttcccgcca ctcttcatgg
 cagcctttga
 421 cgggagacac agccagaccc tgaaggcaat ggtgcaggcc tggcccttca
 cctgcctccc
 40 481 tctgggagtg ctgatgaagg gacaacatct tcacctggag accttcaaag
 ctgtgcttga
 541 tggacttgat gtgtccttg cccaggaggt tcgccccagg aggtggaac
 ttcaagtgt
 601 ggatttacgg aagaactctc atcaggactt ctggactgta tggctctggaa
 45 acagggccag
 661 tctgtactca tttccagagc cagaagcagc tcagcccatg acaaagaagc
 gaaaagtaga
 721 tggtttgagc acagaggcag agcagccctt cattccagta gaggtgctgc
 tagacctgtt
 50 781 cctcaaggaa ggtgcctgtg atgaattgtt ctctacctc attgagaaag
 tgaagcgaaa
 841 gaaaaatgta ctacgcctgt gctgtaagaa gctgaagatt tttgcaatgc
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 55 aagtgacttg
 961 tacctggaag ctaccacact tggcgaaatt ttctccttac ctgggccaga
 tgattaatct

1021 gcgtagactc ctcctctccc acatccatgc atcttcctac atttccccgg
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1081 gcagtatata gccagttca cctctcagtt cctcagtcctg cagtgcctgc
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5 1141 tgtggactct ttatttttcc ttagaggccg cctggatcag ttgctcaggc
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tgccttccct
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ccatatctgc
1501 cttgcagagt ctctgcagc acctcatcgg gctgagcaat ctgaccacg
tgctgtatcc
1561 tgtccccctg gagagttagt aggacatcca tggtaacctc cacctggaga
20 ggcttgcccta
1621 tctgcatgcc aggctcaggg agttgctgtg tgagttgggg cggccagca
tggctctggct
1681 tagtgccaac ccctgtcctc actgtgggga cagaaccttc tatgaccgg
agcccatcct
25 1741 gtgcccctgt ttcatgccta actagctggg tgcacatata aaatgcttca
ttctgcatac
1801 ttggacacta aagccaggat gtgcatgcat cttgaagcaa caaagcagcc
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30 tcagacaaat
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tctaaaggga
35 2041 gattctggct tgggaagtac atgtaggagt taatccctgt gtagactgtt
gtaaagaaac
2101 tgttgaaaat aaagagaagc aatgtgaagc aaaaaaaaaa aaaaaaaaa

40 //

CEA Homo sapiens carcinoembryonic antigen-related cell adhesion
molecule 5 (CEACAM5), mRNA.

ACCESSION NM_004363

45 VERSION NM_004363.1 GI:11386170

SEQ ID NO 88

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50 PNASLLIQNI IQNDTG FYTLHVIKSDLVNEEATGQFRVYPELPKPSISSNNSKPVEDK
DAVAFTCEPETQDATYLWVNNQSLPVS PRLQLSNGNRTLTLFNVTRNDTASYKCETQ

NPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYSWFVNGT
 FQOSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNSNP
 VEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLTLLSVTRNDVGPYE
 CGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYRPGVNLSLSCHAASNPPAQYSWL
 5 IDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTTITVSaelPKPSISSN
 NSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDA
 RAYVCGIQNSVSANRSDPVTLDVLYGPDTPIIISPPDSSYLSGANLNLSCHSASNPSPO
 YSWRINGIPQHTQVLFIKITPNNNGTYACFVSNLATGRNNSIVKSITVSASGTSPG
 LSAGATVGIMIGVLVGVALI"

10

SEQ ID NO 89

ORIGIN

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		gaccatggag				
	121	tctccctcgg	cccctcccca	cagatggtgc	atcccctggc	agaggctcct
		gctcacagcc				
	181	tcaattctaa	ccttctggaa	ccgcccacc	actgccaagc	tcactattga
20		atccacgccg				
	241	ttcaatgtcg	cagaggggaa	ggaggtgctt	ctacttgtcc	acaatctgcc
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Her2/Neu Human tyrosine kinase-type receptor (HER2) mRNA, complete cds.

ACCESSION M11730
VERSION M11730.1 GI:183986
SEQ ID NO 90

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SEQ ID NO 91

ORIGIN Chromosome 17q21-q22.

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H.sapiens mRNA for SCP1 protein.

ACCESSION X95654

VERSION X95654.1 GI:1212982

SEQ ID NO 92

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SEQ ID NO 93

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	2881	aaaaaaggcc	ccttcatctc	taacaacccc	tggacctaca	ctgaagtttg
		gagctataag				

2941 aaaaatgcgg gaggaccgtt gggctgtaat tgctaaaatg gatagaaaaa
 aaaaactaaa
 3001 agaagctgaa aagttatttg ttaatttca gagaatcagt gtagttaagg
 agcctaataa
 5 3061 cgtgaaactt atagttaata ttttgttctt atttgccaga gccacatttt
 atctggaagt
 3121 tgagacttaa aaaatacttg catgaatgat ttgtgtttct ttatattttt
 agcctaaatg
 3181 ttaactacat attgtctgga aacctgtcat tgtattcaga taattagatg
 10 attatatatt
 3241 gttgttactt tttcttgat tcatgaaaac tgtttttact aagttttcaa
 atttgtaaag
 3301 ttagcctttg aatgctagga atgcattatt gagggtcatt ctttattctt
 tactattaaa
 15 3361 atatttttga tgcaaaaaaa aaaaaaaaaa aaa
 //

Homo sapiens synovial sarcoma, X breakpoint 4 (SSX4), mRNA.

20 ACCESSION NM_005636
 VERSION NM_005636.1 GI:5032122
 SEQ ID NO 94

/translation="MNGDDAFARRPRDDAQISEKLRKAFDDIAKYFSKKEWEKMSSEKIVY
 25 VYMKLNYEVMTKLGFKVTLPPFMRSKRAADFHGNDFGNDRNHRNQVERPQMTFG
 SLQRIFPKIMPKKPAEEENGLKEVPEASGPQNDGKQLCPPGNPSTLEKINKTSGPKRG
 KHAWTHRLRERKQLVYEEISDPEEDDE"

SEQ ID NO 95

30 ORIGIN

1 atgaacggag acgacgcctt tgcaaggaga cccagggatg atgctcaa
 atcagagaag
 61 ttacgaaagg ccttogatga tattgccaaa tacttctcta agaaagagt
 ggaaaagatg
 35 121 aaatcctcgg agaaaatcgt ctatgtgtat atgaagctaa actatgaggt
 catgactaaa
 181 ctaggtttca aggtcacct cccaccttc atgcgtagta aacgggctgc
 agacttcac

241 gggaatgatt ttggtaacga tcgaaaccac aggaatcagg ttgaacgtcc
 tcagatgact
 301 ttcggcagcc tccagagaat cttcccgaag atcatgcca agaagccagc
 agaggaagaa
 5 361 aatggtttga aggaagtgcc agaggcatct ggcccacaaa atgatgggaa
 acagctgtgc
 421 cccccgggaa atccaagtac cttggagaag attaacaaga catctggacc
 caaaaggggg
 481 aaacatgcct ggaccacag actgcgtgag agaaagcagc tgggtggttta
 10 tgaagagatc
 541 agcgaccctg aggaagatga cgagtaactc ccctcg

U19142. Human GAGE-1 prot...[gi:914898]

15 LOCUS HSU19142 646 bp mRNA linear
 DEFINITION Human GAGE-1 protein mRNA, complete cds.
 ACCESSION U19142
 VERSION U19142.1 GI:914898

20 SEQ ID No. 96
 /translation="MSWRGRSTYRPRPRRYVEPPEMIGPMRPEQFSDEVEPATPEEGE
 PATQRQDPAAQEGEDEGASAGQGPKEADSQEQGHPQTGCECEDGPDGQEMDPPNPE
 EVKTPEEEMRSHYVAQTGILWLLMNNCFNLNSPRKP"

25 SEQ ID NO. 97
 1 ctgccgtccg gactcttttt cctctactga gattcatctg tgtgaaatat
 gagttggcga
 61 ggaagatcga cctatcggcc tagaccaaga cgctacgtag agcctcctga
 30 aatgattggg
 121 cctatgcggc ccgagcagtt cagtgatgaa gtggaaccag caacacctga
 agaaggggaa
 181 ccagcaactc aacgtcagga tcctgcagct gctcaggagg gagaggatga
 gggagcatct
 35 241 gcaggtaag ggccgaagcc tgaagctgat agccaggaac agggtcaccc
 acagactggg
 301 tgtgagtgtg aagatgggtcc tgatgggcag gagatggacc cgccaaatcc
 agaggaggtg

361 aaaacgcctg aagaagagat gaggtctcac tatgttgccc agactgggat
tctctggctt
421 ttaatgaaca attgcttctt aaatctttcc ccacggaaac cttgagtga
tgaaatatca
5 481 aatggcgaga gaccgtttag ttcctatcat ctgtggcatg tgaagggcaa
tcacagtgtt
541 aaaagaagac atgctgaaat gttgcaggct gctcctatgt tggaaaattc
ttcattgaag
601 ttctcccaat aaagctttac agccttctgc aaagaaaaaa aaaaaa
10 //

NM_001168. Homo sapiens bacu...[gi:4502144]
LOCUS BIRC5 1619 bp mRNA linear
DEFINITION Homo sapiens baculoviral IAP repeat-containing 5
15 (survivin) (BIRC5), mRNA.
ACCESSION NM_001168
VERSION NM_001168.1 GI:4502144

SEQ ID NO. 98
20 /translation="MGAPTLPPAWQPFLKDHRISTFKNWPFLGCACTPERMAEAGFI
HCPTENEPDLAQCFFCFKELEGWEPDDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFL
KLDREERAKNKIAKETNNKKKEFEETAKKVRRAIEQLAAMD"

25 SEQ ID NO. 99
1 ccgccagatt tgaatcgcg gaccggttg cagaggtggc ggcggcggca
tggttgcccc
61 gacgttgccc cctgctggc agccctttct caaggaccac cgcattctta
cattcaagaa
30 121 ctggcccttc ttggagggt ggcctgcac cccggagcgg atggccgagg
ctggcttcat
181 ccactgcccc actgagaacg agccagactt ggcccagtgt ttcttctgct
tcaaggagct
241 ggaaggctgg gagccagatg acgaccccat agaggaacat aaaaagcatt
35 cgtccggttg
301 cgctttcctt tctgtcaaga agcagtttga agaattaacc cttggtgaat
ttttgaaact
361 ggacagagaa agagccaaga acaaaattgc aaaggaaacc aacaataaga
agaaagaatt

421 tgaggaaact gcgaagaaag tgcgccgtgc catcgagcag ctggctgcca
 tggattgagg
 481 cctctggccg gagctgcctg gtcccagagt ggctgcacca cttccaggg
 ttattccctg
 5 541 gtgccaccag ccttcctgtg ggccccttag caatgtctta ggaaaggaga
 tcaacatttt
 601 caaattagat gtttcaactg tgctcctggt ttgtcttgaa agtggcacca
 gaggtgcttc
 661 tgccgtgca gcgggtgctg ctggtaacag tggctgcttc tctctctctc
 10 tctctttttt
 721 gggggctcat ttttgctggt ttgattcccg ggcttaccag gtgagaagt
 agggaggaag
 781 aaggcagtgt cccttttgct agagctgaca gctttgttcg cgtgggcaga
 gccttcaca
 15 841 gtgaatgtgt ctggacctca tgttggtgag gctgtcacag tcctgagtgt
 ggacttgga
 901 ggtgcctggt gaatctgagc tgcaggttcc ttatctgtca cacctgtgcc
 tcctcagagg
 961 acagtttttt tgttggtgtg tttttttggt tttttttttt ggtagatgca
 20 tgacttgtgt
 1021 gtgatgagag aatggagaca gaggccctgg ctccctact gttaacaac
 atggctttct
 1081 ttttttgttt gaattgttaa ttcacagaat agcacaact acaattaaaa
 ctaagcacia
 25 1141 agccattcta agtcattggg gaaacggggg gaacttcagg tggatgagga
 gacagaatag
 1201 agtgatagga agcgtctggc agatactcct tttgccactg ctgtgtgatt
 agacaggccc
 1261 agtgagccgc ggggcacatg ctggccgctc ctccctcaga aaaaggcagt
 30 ggcctaaatc
 1321 cttttttaa atgacttggtc gatgctgtgg gggactggct gggctgctgc
 aggccgtgtg
 1381 tctgtcagcc caaccttcac atctgtcacg ttctccacac gggggagaga
 cgcagtcgc
 35 1441 ccagggtccc gctttctttg gaggcagcag ctcccgagg gctgaagtct
 ggcgtaagat
 1501 gatggatttg attcgccctc ctccctgtca tagagctgca ggggtggattg
 ttacagcttc

1561 gctggaaacc tctggaggctc atctcggctg ttcttgagaa ataaaaagcc
tgtcatttc
//

5

U06452. Human melanoma an...[gi:476131]

LOCUS HSU06452 1524 bp mRNA linear

DEFINITION Human melanoma antigen recognized by T-cells (MART-1)
mRNA.

10 ACCESSION U06452

VERSION U06452.1 GI:476131

SEQ ID NO.100

/translation="MPREDAHFYGYPKKGHGHSTTAEEAAGIGILTVILGVLLIG

15

CWYCRRRNGYRALMDKSLHVGTTQCALTRRCPEGFDHRDSKVSLEKNCEPVVPNAPP
AYEKLSAEQSPPPYSP"

SEQ ID NO. 101

20 1 agcagacaga ggactctcat taaggaaggt gtcctgtgcc ctgaccctac
aagatgccaa
61 gagaagatgc tcacttcac tatggttacc ccaagaaggg gcacggccac
tcttacacca
121 cggctgaaga ggccgctggg atcggcatcc tgacagtgat cctgggagtc
25 ttactgctca
181 tcggctgttg gtattgtaga agacgaaatg gatacagagc cttgatggat
aaaagtcttc
241 atgttggcac tcaatgtgcc ttaacaagaa gatgccacaca agaagggttt
gatcatcggg
30 301 acagcaaagt gtctcttcaa gagaaaaact gtgaacctgt ggttcccaat
gctccacctg
361 cttatgagaa actctctgca gaacagtcac caccacctta ttcaccttaa
gagccagcga
421 gacacctgag acatgctgaa attatttctc tcacactttt gcttgaattt
35 aatacagaca
481 tctaattgtc tcctttggaa tgggtgtagga aaaatgcaag ccatctctaa
taataagtca
541 gtgttaaaat tttagtaggt cggctagcag tactaatcat gtgaggaaat
gatgagaaat


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        601 attaaattgg gaaaactcca tcaataaatg ttgcaatgca tgatactatc
        tgtgccagag
        661 gtaatgtag taaatccatg gtgttatatt ctgagagaca gaattcaagt
        gggtagtctg
5       721 gggccatcca atttctcttt acttgaaatt tggctaataa caaactagtc
        aggttttcga
        781 accttgaccg acatgaactg tacacagaat tgttccagta ctatggagtg
        ctcacaaagg
        841 atacttttac aggttaagac aaagggttga ctggcctatt tatctgatca
10      agaàcatgtc
        901 agcaatgtct ctttgtgctc taaaattcta ttatactaca ataatatatt
        gtaaagatcc
        961 tatagctctt tttttttgag atggagtttc gcttttggtg cccaggctgg
        agtgcaatgg
15      1021 cgcgatcttg gctcaccata acctccgcct cccaggttca agcaattctc
        ctgccttagc
        1081 ctcttgagta gctgggatta caggcgtgcg ccactatgcc tgactaattt
        tgtagtttta
        1141 gtagagacgg ggtttctcca tgttggtcag gctggtctca aactcctgac
20      ctcaggtgat
        1201 ctgcccgcct cagcctccca aagtgtgga attacaggcg tgagccacca
        cgcctggctg
        1261 gatcctatat cttaggtaag acatataacg cagtctaatt acatttcact
        tcaaggctca
25      1321 atgctattct aactaatgac aagtattttc tactaaacca gaaattggta
        gaaggattta
        1381 aataagtaaa agctactatg tactgcctta gtgctgatgc ctgtgtactg
        ccttaaattgt
        1441 acctatggca atttagctct cttgggttcc caaatccctc tcacaagaat
30      gtgcagaaga
        1501 aatcataaag gatcagagat tctg
        //

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U19180. Human B melanoma ...[gi:726039]

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35  LOCUS      HSU19180                1004 bp    mRNA    linear
      DEFINITION Human B melanoma antigen (BAGE) mRNA, complete cds.
      ACCESSION  U19180
      VERSION    U19180.1  GI:726039

```

SEQ IS NO. 102

/translation="MAARAVFLALSAQLLQARLMKEESPVSWRLEPEDGTALCFIF"

SEQ ID NO. 103

```
5           1  cgccaattta  ggggtctccgg  tatctcccgc  tgagctgctc  tgttcccggc
            ttagaggacc
            61  aggagaaggg  ggagctggag  gctggagcct  gtaacaccgt  ggctcgtctc
            actctggatg
            121  gtggtggcaa  cagagatggc  agcgcagctg  gagtgttagg  agggcggcct
10  gagcggtagg
            181  agtggggctg  gagcagtaag  atggcggcca  gagcggtttt  tctggcattg
            tctgcccagc
            241  tgctccaagc  caggctgatg  aaggaggagt  cccctgtggg  gagctggagg
            ttggagcctg
15           301  aagaaggcac  agctctgtgc  ttcattctct  gaggttgctg  cagccacggt
            gatggagacg
            361  gcagctcaac  aggagcaata  ggaggagatg  gagtttcact  gtgtcagcca
            ggatggtctc
            421  gatctcctga  cctcgtgatc  cgcccgccct  ggccttccaa  agtgccgaga
20  ttacagcgat
            481  gtgcattttg  taagcacttt  ggagccacta  tcaaagtctg  tgaagagaaa
            tgtaccaga
            541  tgtatcatta  tccttggtgt  gcaggagccg  gtccttttca  ggatttcagt
            cacatcttcc
25           601  tgctttgtcc  agaacacatt  gaccaagctc  ctgaaagatg  taagtttact
            acgcatagac
            661  ttttaaactt  caaccaatgt  atttactgaa  aataacaaat  gttgtaaatt
            ccctgagtgt
            721  tattctactt  gtattaaaag  gtaataatac  ataatcatta  aaatctgagg
30  gatcattgcc
            781  agagattggt  ggggagggaa  atgttatcaa  cggtttcatt  gaaattaaat
            ccqaaaagtt
            841  atttcctcag  aaaaatcaaa  taaagtttgc  atgtttttta  ttcttaaaac
            attttaaaaa
35           901  ccactgtaga  atgatgtaaa  tagggactgt  gcagtatttc  tgacatatac
            tataaaatta
            961  ttaaaaagtc  aatcagtatt  caacatcttt  tacactaaaa  agcc
//
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The teachings and embodiments disclosed in any of the publications, including patents, patent publications and non-patent publications, disclosed herein are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

5 The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should
10 be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of the embodiments of this invention.

15

WHAT IS CLAIMED IS:

1. A polypeptide, comprising a component selected from the group consisting of:
 - (i) a polypeptide epitope having the sequence as disclosed in TABLE 1B;
 - (ii) an epitope cluster comprising the polypeptide of (i);
 - (iii) a polypeptide having substantial similarity to (i) or (ii);
 - (iv) a polypeptide having functional similarity to any of (i) through (iii); and
 - (v) a nucleic acid encoding the polypeptide of any of (i) through (iv).
2. The polypeptide of claim 1, wherein the polypeptide is immunologically active.
3. The polypeptide of claim 1, wherein the polypeptide is less than about 30 amino acids in length.
4. The polypeptide of claim 1, wherein the polypeptide is 8 to 10 amino acids in length.
5. The polypeptide of claim 1, wherein the substantial or functional similarity comprises addition of at least one amino acid.
6. The polypeptide of claim 5, wherein the at least one additional amino acid is at an N-terminus of the polypeptide.
7. The polypeptide of claim 1, wherein the substantial or functional similarity comprises a substitution of at least one amino acid.
8. The polypeptide of claim 1, the polypeptide having affinity to an HLA-A2 molecule.
9. The polypeptide of claim 8, wherein the affinity is determined by an assay of binding.
10. The polypeptide of claim 8, wherein the affinity is determined by an assay of restriction of epitope recognition.
11. The polypeptide of claim 8, wherein the affinity is determined by a prediction algorithm.
12. The polypeptide of claim 1, the polypeptide having affinity to an HLA-B7 or HLA-B51 molecule.
13. The polypeptide of claim 1, wherein the polypeptide is a housekeeping epitope.
14. The polypeptide of claim 1, wherein the polypeptide corresponds to an epitope displayed on a tumor cell.
15. The polypeptide of claim 1, wherein the polypeptide corresponds to an epitope displayed on a neovasculature cell.
16. The polypeptide of claim 1, wherein the polypeptide is an immune epitope.
17. The polypeptide of claim 1, wherein the polypeptide is encoded by a nucleic acid.

18. A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.
19. The composition of claim 18, where the adjuvant is a polynucleotide.
20. The composition of claim 19 wherein the polynucleotide comprises a dinucleotide.
21. The composition of claim 20 wherein the dinucleotide is CpG.
22. The composition of claim 18, wherein the adjuvant is encoded by a polynucleotide.
23. The composition of claim 18 wherein the adjuvant is a cytokine.
24. The composition of claim 23 wherein the cytokine is GM-CSF.
25. The composition of claim 18 further comprising a professional antigen-presenting cell (pAPC).
26. The composition of claim 25, wherein the pAPC is a dendritic cell.
27. The composition of claim 18, further comprising a second epitope.
28. The composition of claim 27, wherein the second epitope is a polypeptide.
29. The composition of claim 27, wherein the second epitope is a nucleic acid.
30. The composition of claim 27, wherein the second epitope is a housekeeping epitope.
31. The composition of claim 27, wherein the second epitope is an immune epitope.
32. A composition comprising the nucleic acid of claim 1 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.
33. A recombinant construct comprising the nucleic acid of Claim 1.
34. The construct of claim 33, further comprising a plasmid, a viral vector, a bacterial vector, or an artificial chromosome.
35. The construct of claim 33, further comprising a sequence encoding at least one feature selected from the group consisting of a second epitope, an IRES, an ISS, an NIS, and ubiquitin.
36. A purified antibody that specifically binds to the polypeptide of claim 1.
37. A purified antibody that specifically binds to a peptide-MHC protein complex comprising the polypeptide of claim 1.
38. The antibody of claim 36 or claim 37, wherein the antibody is a monoclonal antibody.
39. A multimeric MHC-peptide complex comprising the polypeptide of claim 1.
40. An isolated T cell expressing a T cell receptor specific for an MHC-peptide complex, the complex comprising the polypeptide of claim 1.
41. The T cell of claim 40, produced by an *in vitro* immunization.
42. The T cell of claim 40, isolated from an immunized animal.
43. A T cell clone comprising the T cell of claim 40.

44. A polyclonal population of T cells comprising the T cell of claim 40.
45. A pharmaceutical composition comprising the T cell of claim 40 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.
46. An isolated protein molecule comprising the binding domain of a T cell receptor specific for an MHC-peptide complex, the complex comprising the epitope of claim 1.
47. The protein of claim 46, wherein the protein is multivalent.
48. An isolated nucleic acid encoding the protein of claim 46.
49. A recombinant construct comprising the nucleic acid of claim 48.
50. A host cell expressing a recombinant construct, the construct comprising the nucleic acid of claim 1, or the construct encoding a protein molecule comprising the binding domain of a T cell receptor specific for an MHC-peptide complex.
51. The host cell of claim 50, wherein the host cell is a dendritic cell, macrophage, tumor cell, or tumor-derived cell.
52. The host cell of claim 50, wherein the host cell is a bacterium, fungus, or protozoan.
53. A composition comprising the host cell of claim 50 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.
54. A composition comprising at least one component selected from the group consisting of the epitope of claim 1; the composition of claim 18, 32, or 45, the construct of claim 33; the T cell of claim 40, a host cell expressing a recombinant construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex and a composition comprising the same, and a host cell expressing a recombinant construct comprising the nucleic acid of claim 1 and a composition comprising the same.
55. A method of treating an animal, comprising:
administering to an animal the composition of claim 54.
56. The method of claim 55, wherein the administering step comprises a mode of delivery selected from the group consisting of transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, mucosal, aerosol inhalation, and instillation.
57. The method of claim 55, further comprising a step of assaying to determine a characteristic indicative of a state of a target cell or target cells.
58. The method of claim 57, comprising a first assaying step and a second assaying step, wherein the first assaying step precedes the administering step, and wherein the second assaying step follows the administering step.
59. The method of claim 58, further comprising a step of comparing the characteristic determined in the first assaying step with the characteristic determined in the second assaying step to obtain a result.

60. The method of claim 59, wherein the result is selected from the group consisting of: evidence of an immune response, a diminution in number of target cells, a loss of mass or size of a tumor comprising target cells, a decrease in number or concentration of an intracellular parasite infecting target cells.
61. A method of evaluating immunogenicity of an immunogenic composition, comprising:
administering to an animal the composition of claim 54; and
evaluating immunogenicity based on a characteristic of the animal.
62. The method of claim 61, wherein the animal is MHC-transgenic.
63. A method of evaluating immunogenicity, comprising:
in vitro stimulation of a T cell with the composition of claim 54; and
evaluating immunogenicity based on a characteristic of the T cell.
64. The method of claim 63, wherein the stimulation is a primary stimulation.
65. A method of making a passive/adoptive immunotherapeutic, comprising:
combining the T cell of claim 40, or a host cell expressing a recombinant construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex, or a host cell expressing a recombinant construct comprising the nucleic acid of claim 1 with a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.
66. A method of determining specific T cell frequency comprising the step of contacting T cells with a MHC-peptide complex comprising the polypeptide of claim 1.
67. The method of claim 66, wherein the contacting step comprises at least one feature selected from the group consisting of immunization, restimulation, detection, and enumeration.
68. The method of Claim 66, further comprising ELISPOT analysis, limiting dilution analysis, flow cytometry, *in situ* hybridization, the polymerase chain reaction or any combination thereof.
69. A method of evaluating immunologic response, comprising the method of claim 66 carried out prior to and subsequent to an immunization step.
70. A method of evaluating immunologic response, comprising:
determining frequency, cytokine production, or cytolytic activity of T cells, prior to and subsequent to a step of stimulation with MHC-peptide complexes comprising the polypeptide of claim 1.
71. A method of diagnosing a disease comprising:
contacting a subject tissue with at least one component selected from the group consisting of the T cell of claim 40, the host cell of claim 50, the antibody of claim 36, and the protein of claim 46; and

diagnosing the disease based on a characteristic of the tissue or of the component.

72. The method of claim 71, wherein the contacting step takes place *in vivo*.

73. The method of claim 71, wherein the contacting step takes place *in vitro*.

74. A method of making a vaccine, comprising:

combining at least one component selected from the group consisting of the polypeptide of claim 1; the composition of claim 18, 32, 45, or 53; the construct of claim 33; the T cell of claim 40, and the host cell of claim 50, with a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

75. A computer readable medium having recorded thereon the sequence of any one of SEQ ID NOS: 108-610, in a machine having a hardware or software that calculates the physical, biochemical, immunologic, or molecular genetic properties of a molecule embodying said sequence.

76. A method of treating an animal comprising combining the method of claim 55 combined with at least one mode of treatment selected from the group of radiation therapy, chemotherapy, biochemotherapy, and surgery.

77. An isolated polypeptide comprising an epitope cluster from a target-associated antigen having the sequence as disclosed in Tables 68-73, wherein the amino acid sequence consists of not more than about 80% of the amino acid sequence of the antigen.

78. A vaccine or immunotherapeutic product comprising the polypeptide of claim 77.

79. An isolated polynucleotide encoding the polypeptide of claim 77.

80. A vaccine or immunotherapeutic product comprising the polynucleotide of claim 79.

81. The polynucleotide of claim 79 or 80, wherein the polynucleotide is DNA.

82. The polynucleotide of claim 79 or 80, wherein the polynucleotide is RNA.

FIG. 1B

CTAG_HUMAN	NY-ESO	(101)	101	150
AAD05202	- CAG-3	(101)	101	150
CAA11044	- LAGE-1a	(101)	101	150
CAA10194	- LAGE-1s	(101)	101	150
CAA11043	- LAGE-1b	(101)	101	150
CAA10196	- LAGE-1L	(101)	101	150
AAH02833	CT-2	(101)	101	150
Consensus		(101)	101	150
CTAG_HUMAN	NY-ESO	(151)	151	200
AAD05202	- CAG-3	(151)	151	200
CAA11044	- LAGE-1a	(151)	151	200
CAA10194	- LAGE-1s	(151)	151	200
CAA11043	- LAGE-1b	(151)	151	200
CAA10196	- LAGE-1L	(151)	151	200
AAH02833	CT-2	(151)	151	200
Consensus		(151)	151	200

FIG. 1C

CTAG_HUMAN	NY-ESO	(181)	-----
AAD05202	- CAG-3	(181)	-----
CAA11044	-LAGE-1a	(181)	-----
CAA10194	- LAGE-1s	(181)	-----
CAA11043	- LAGE-1b	(201)	FNVMSAPHI
CAA10196	- LAGE-1L	(201)	FNVMSAPHI
AAH02833	CT-2	(201)	FNVMSAPHI
	Consensus	(201)	

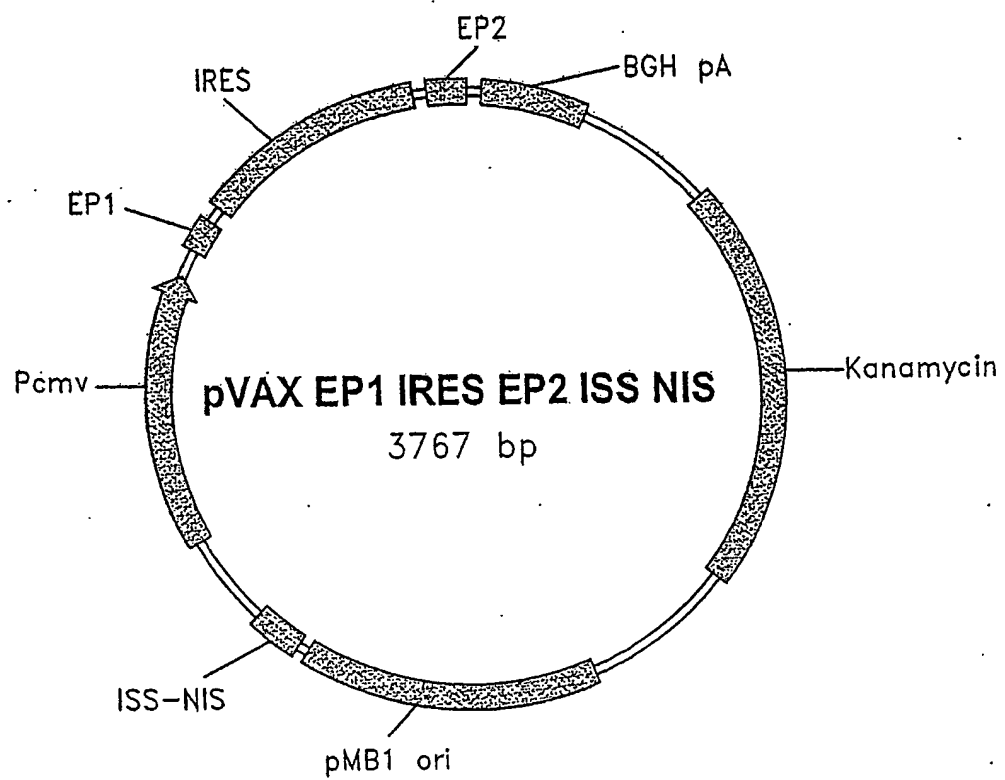
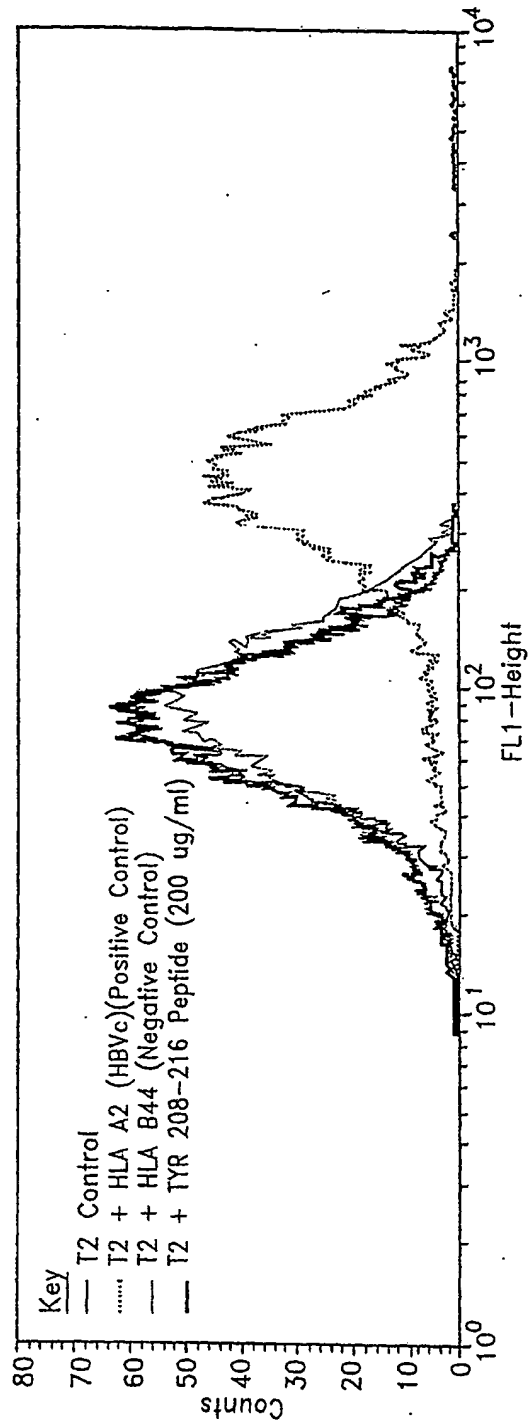
*FIG. 2*

FIG. 3A

FACscan Analysis of Binding Assay to Determine the Binding Ability of Tyrosinase 208-216 Peptide to MHC Class 1

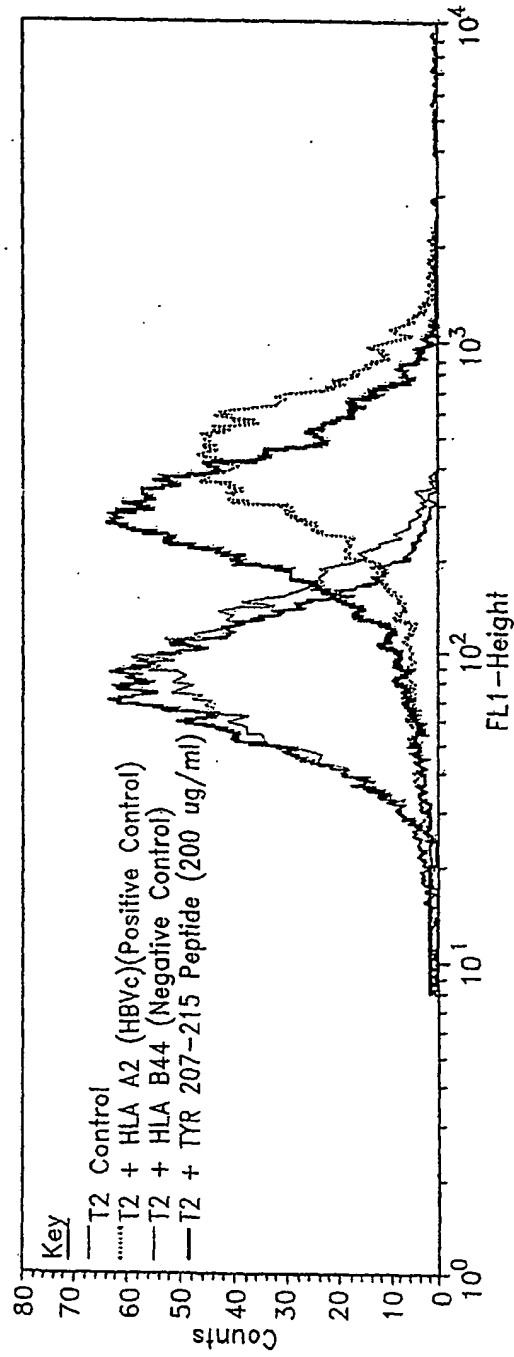


F1 (HLA A2 Peptide) = 3.13

F1 (TYR 208-216 Peptide) = 0.01

FIG. 3B

**FACscan Analysis of Binding Assay to Determine the Binding
Ability of Tyrosinase 207-215 Peptide to MHC Class 1**

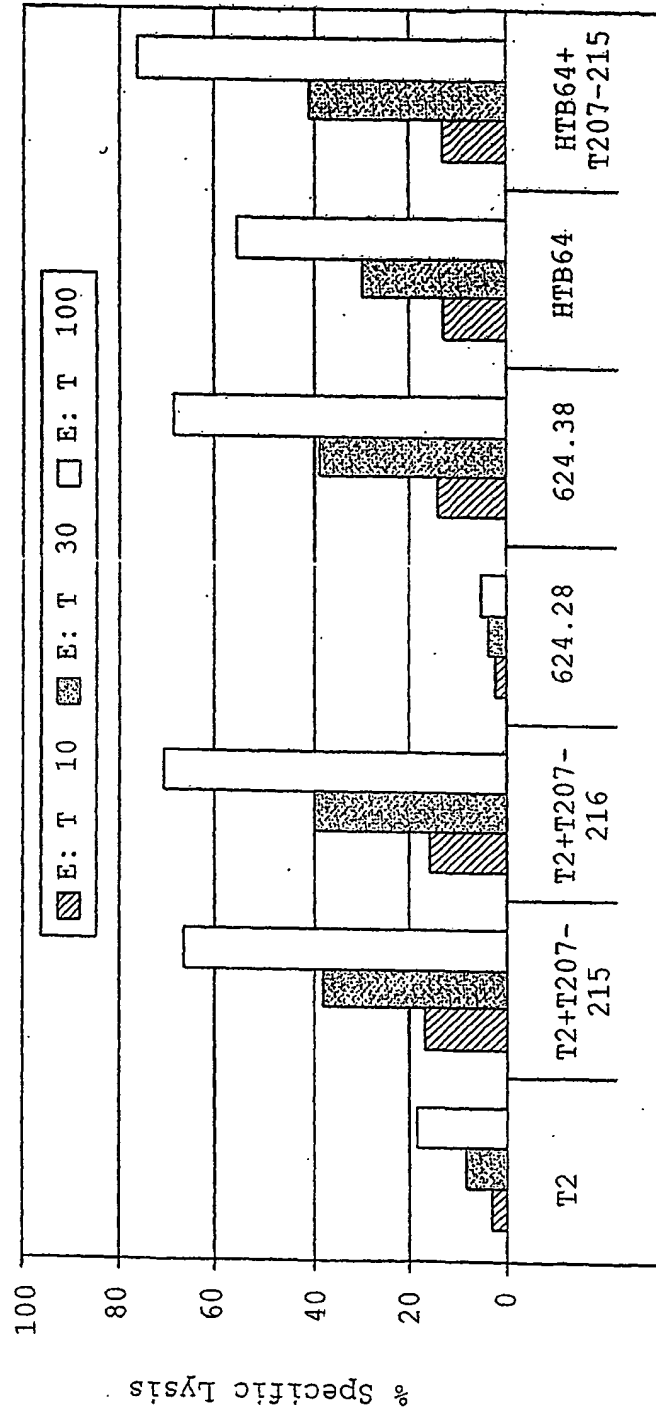


F1 (HLA A2 Peptide) = 3.13

F1 (TYR 207-215 Peptide) = 2.00

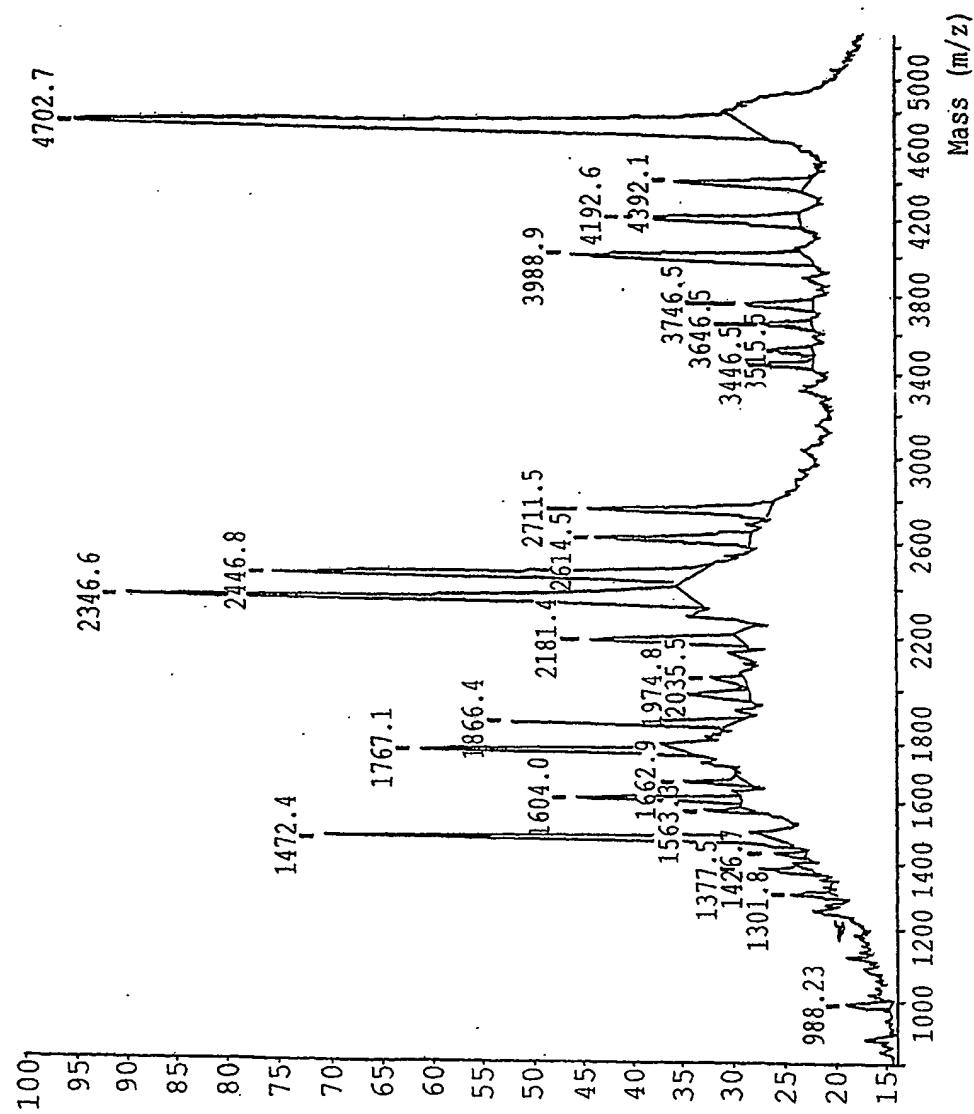
FIG. 3C

HLA A2 restricted and tyrosinase specific lysis by
CTL from Tyr207-215 IVS blood



CTL from Tyr 207-215 IVS blood

FIG. 4



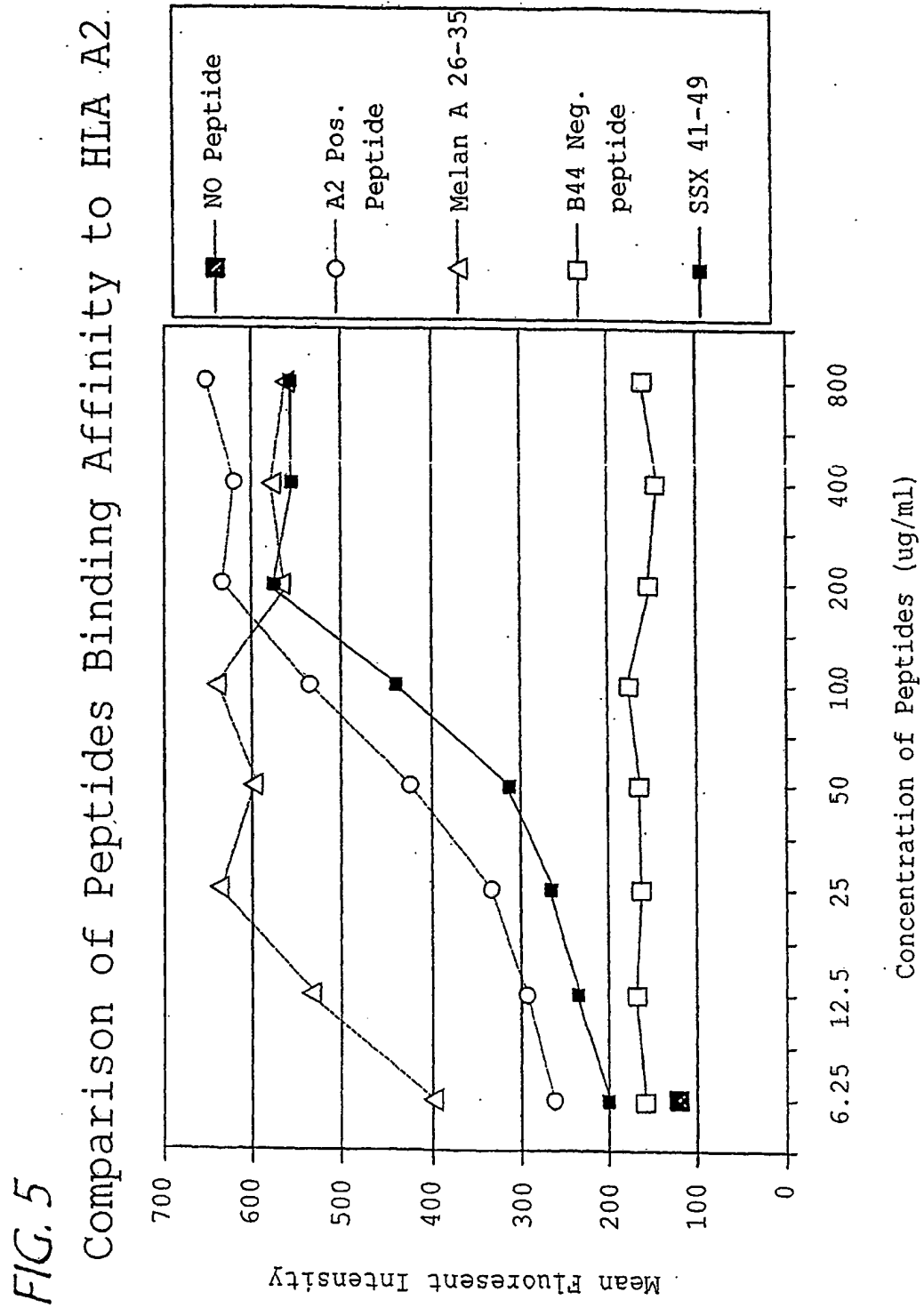


FIG. 6
SSX2₄₁₋₄₉ specific lysis by CTL from peptide
injected HHD1 mice

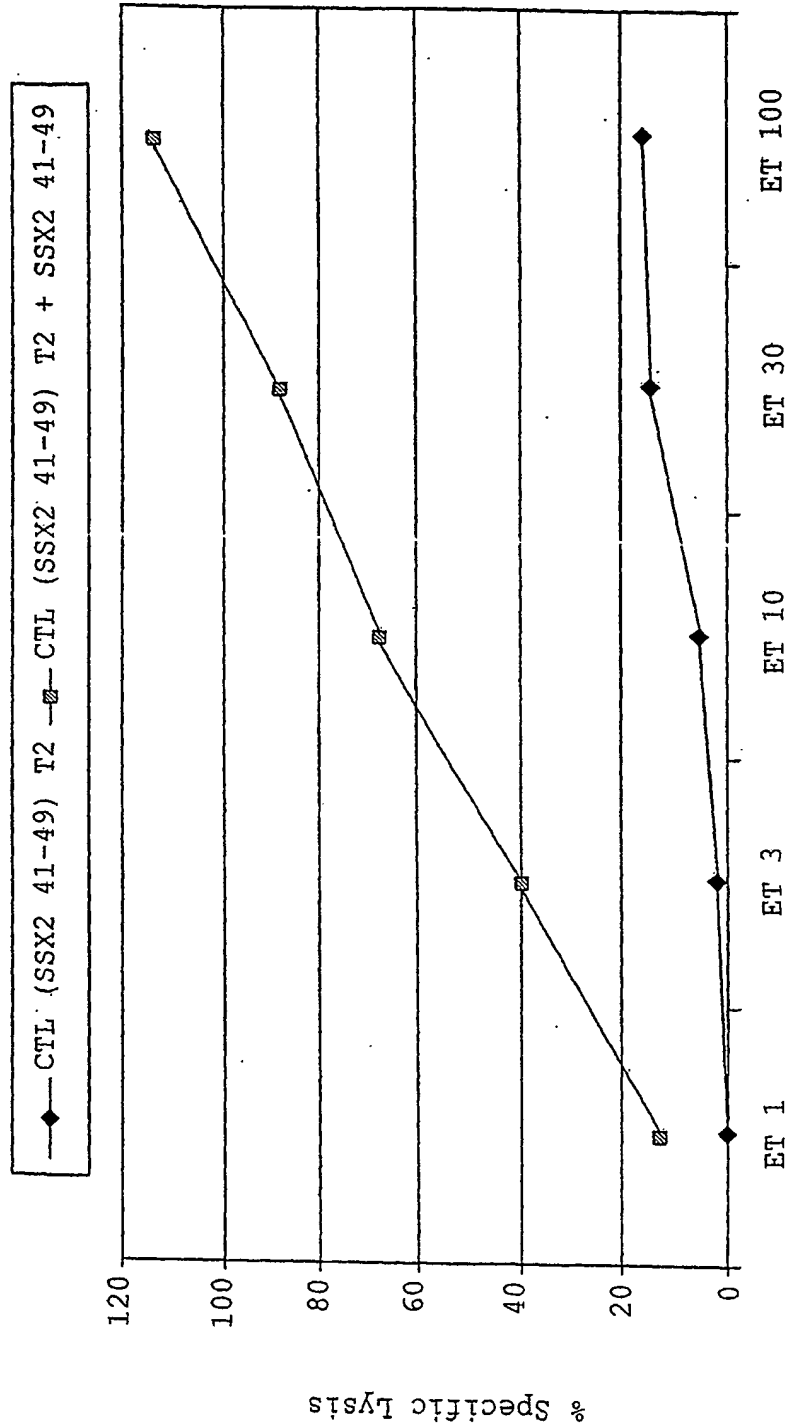
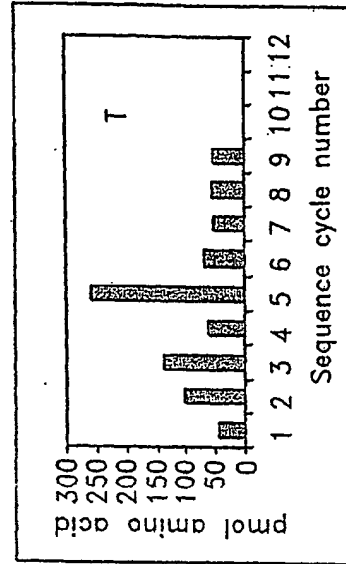
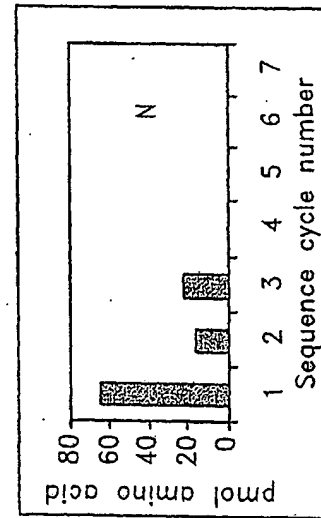
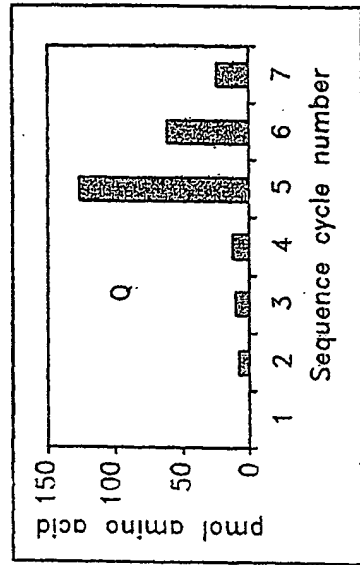
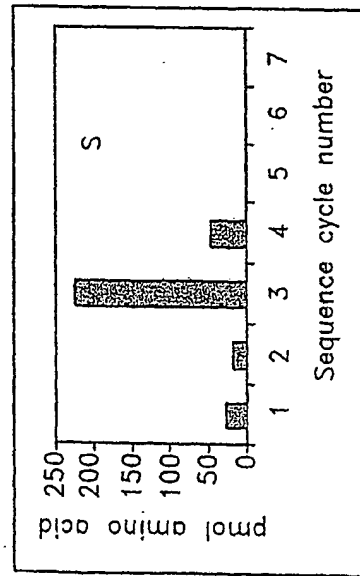
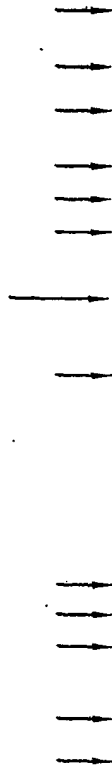


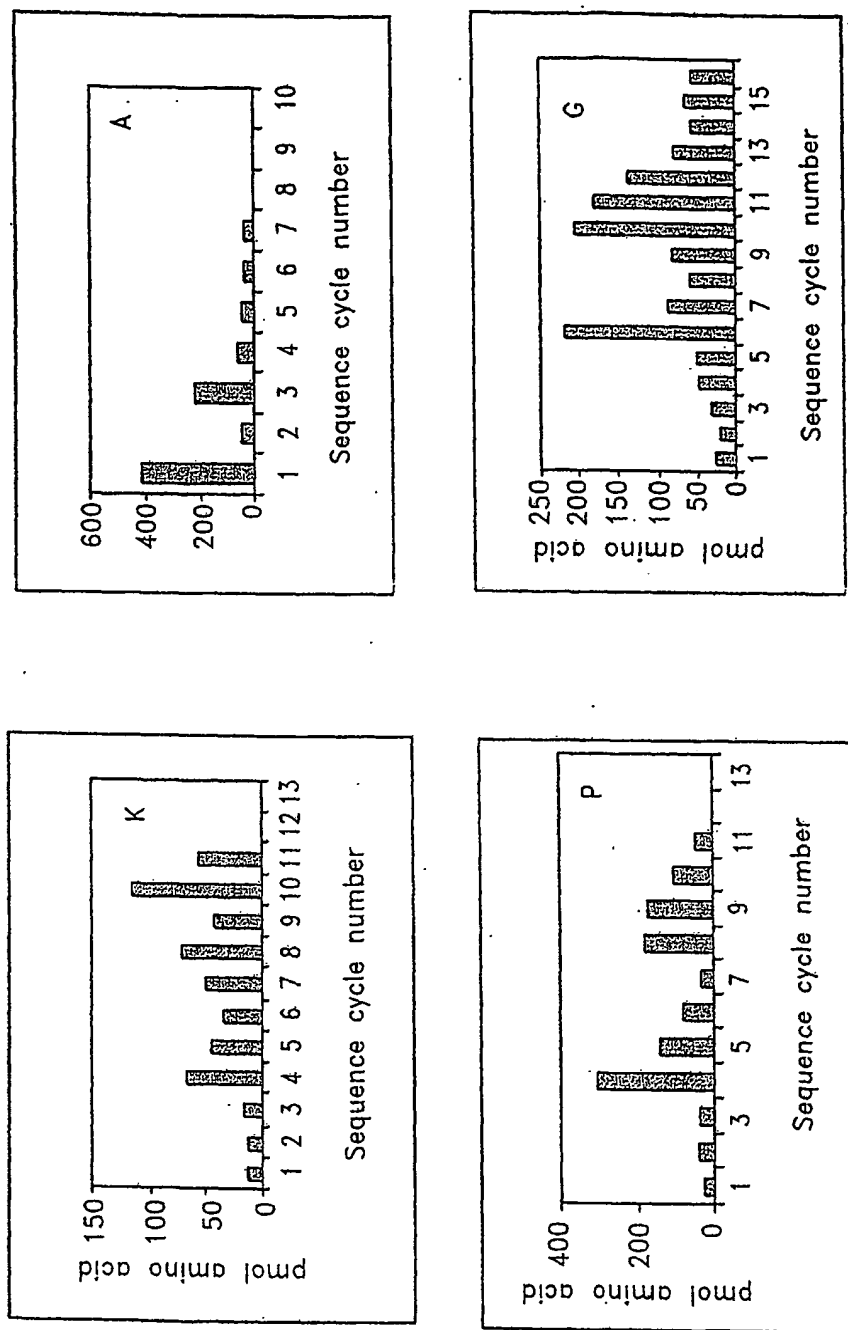
FIG. 7A

163-AFSPQGMPEGLVYV**N**YARTEDEFFKLERDM-192

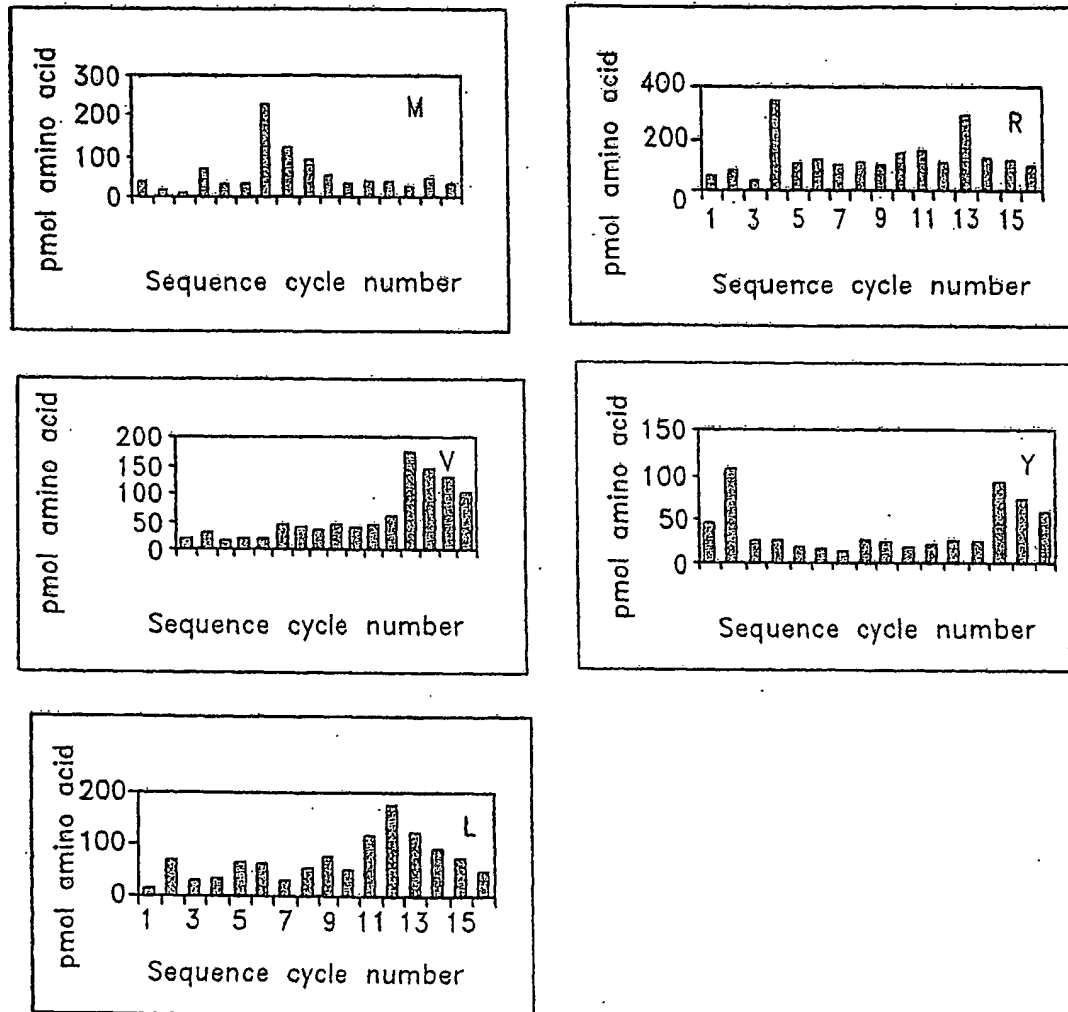


Pool sequencing of PSMA_163-192 Digested for 60 min by proteasome

FIG. 7B



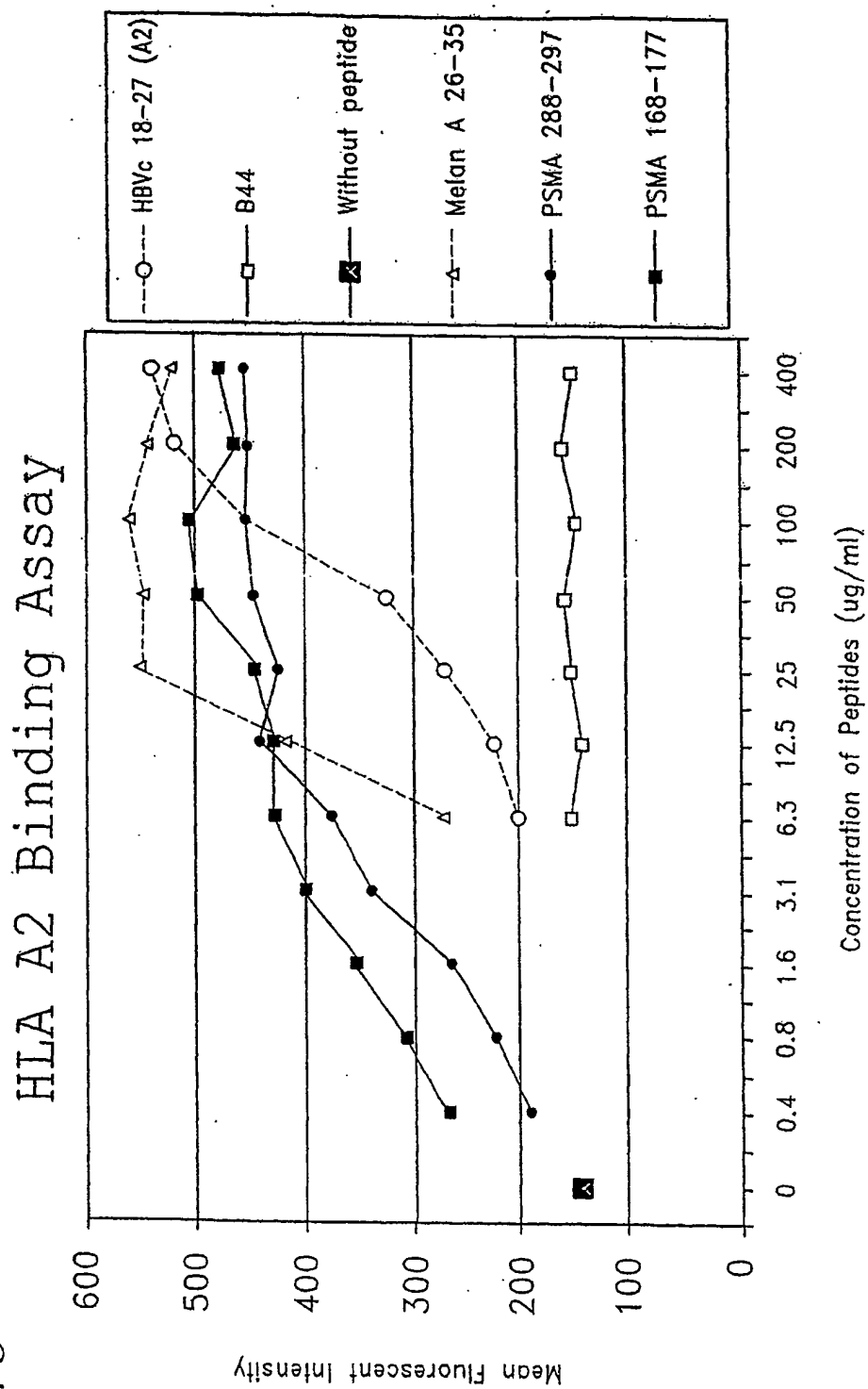
Pool sequencing of PSMA_163-192 Digested for 60 min by proteasome

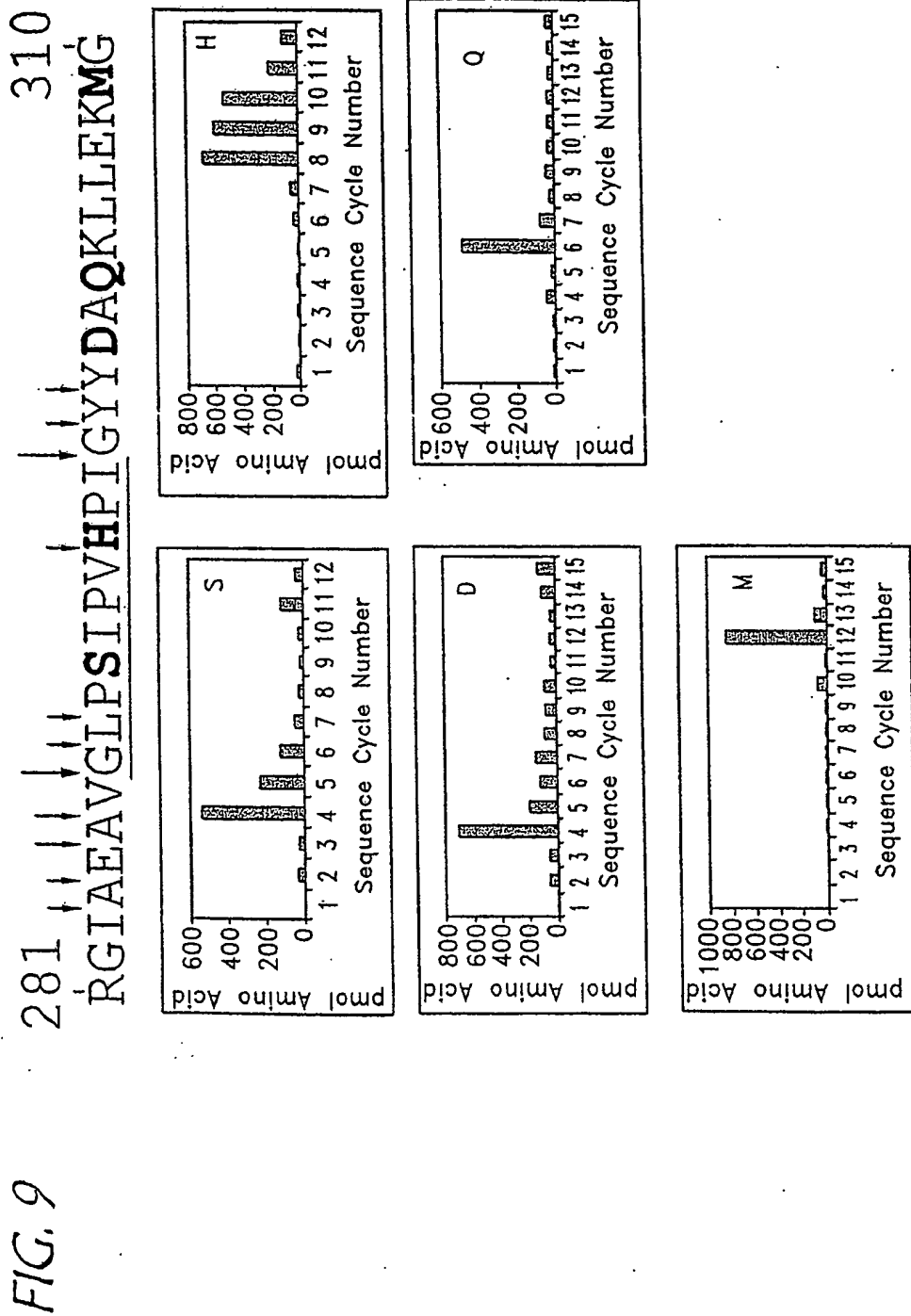


Pool sequencing of PSMA_163-192 Digested for 60 min by proteasome

FIG. 7C

FIG. 8

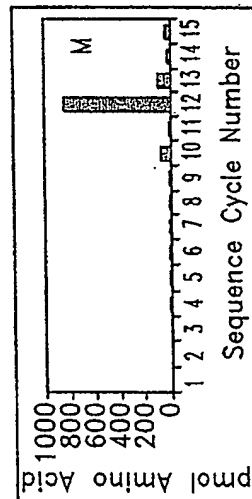
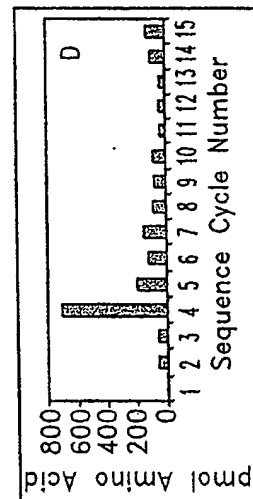
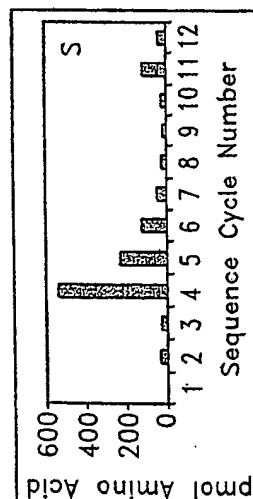
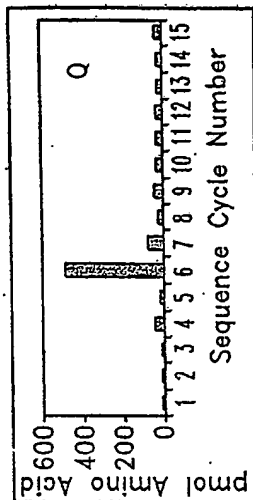
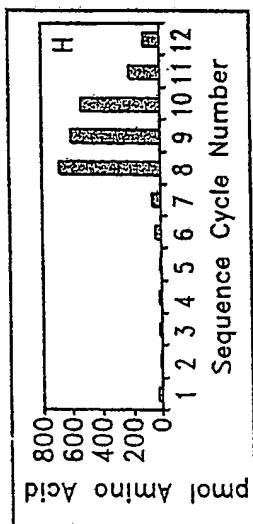




310

281

RGIAEAVGLPSIPVHPICY^YDAQKLEKMG



Pool sequencing of PSMA_281_310 Digested for 60 min by Proteasome

Autologous DC Present A1 Peptide to CD8 T cell

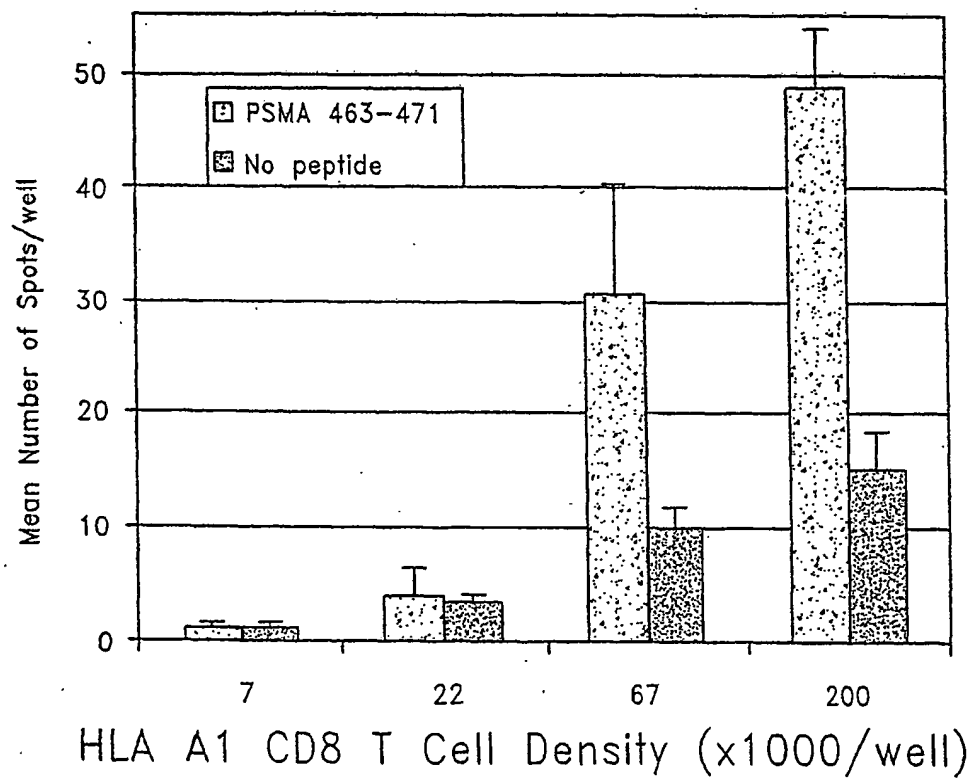


FIG. 11

Secretion of IFN γ Was Blocked by Anti-A1 Antibody

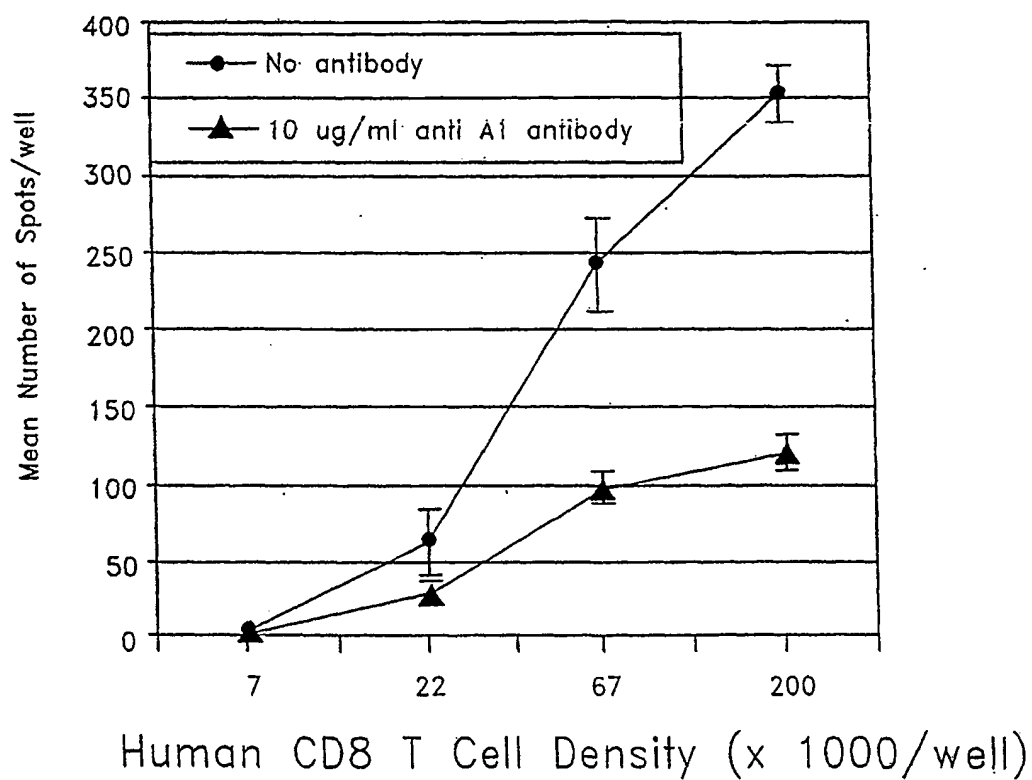


FIG. 12

FIG. 13
Comparison of Peptides Binding Affinity
to HLA A2 by Binding Assay

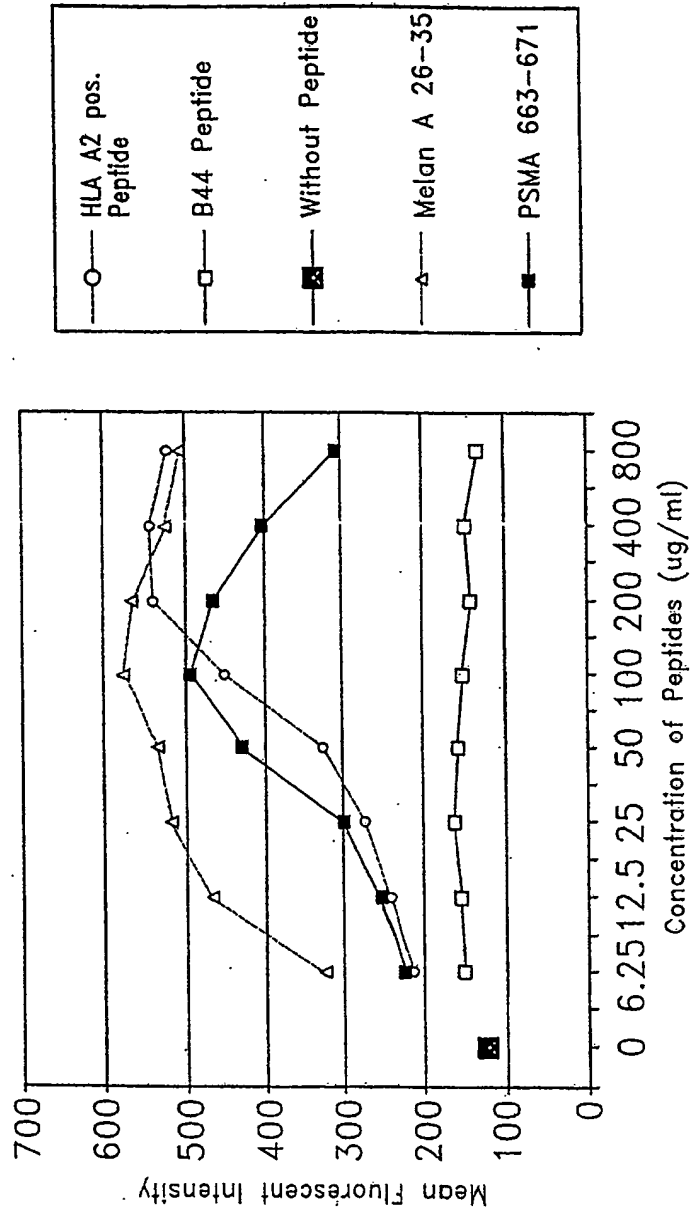
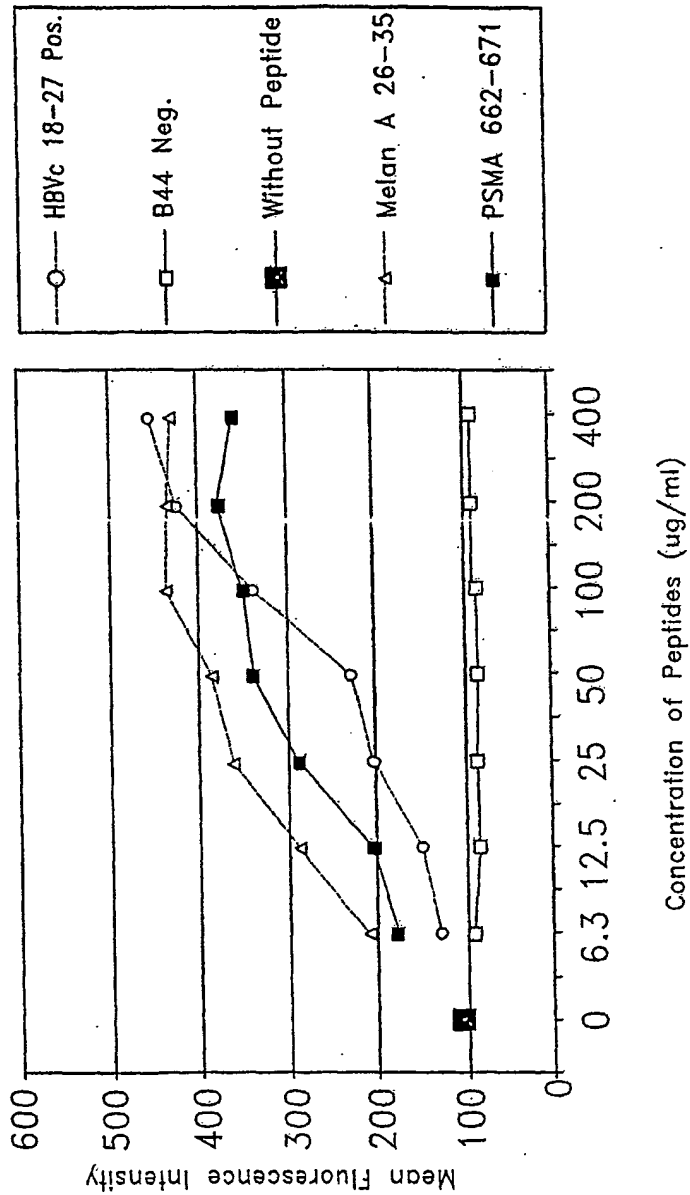
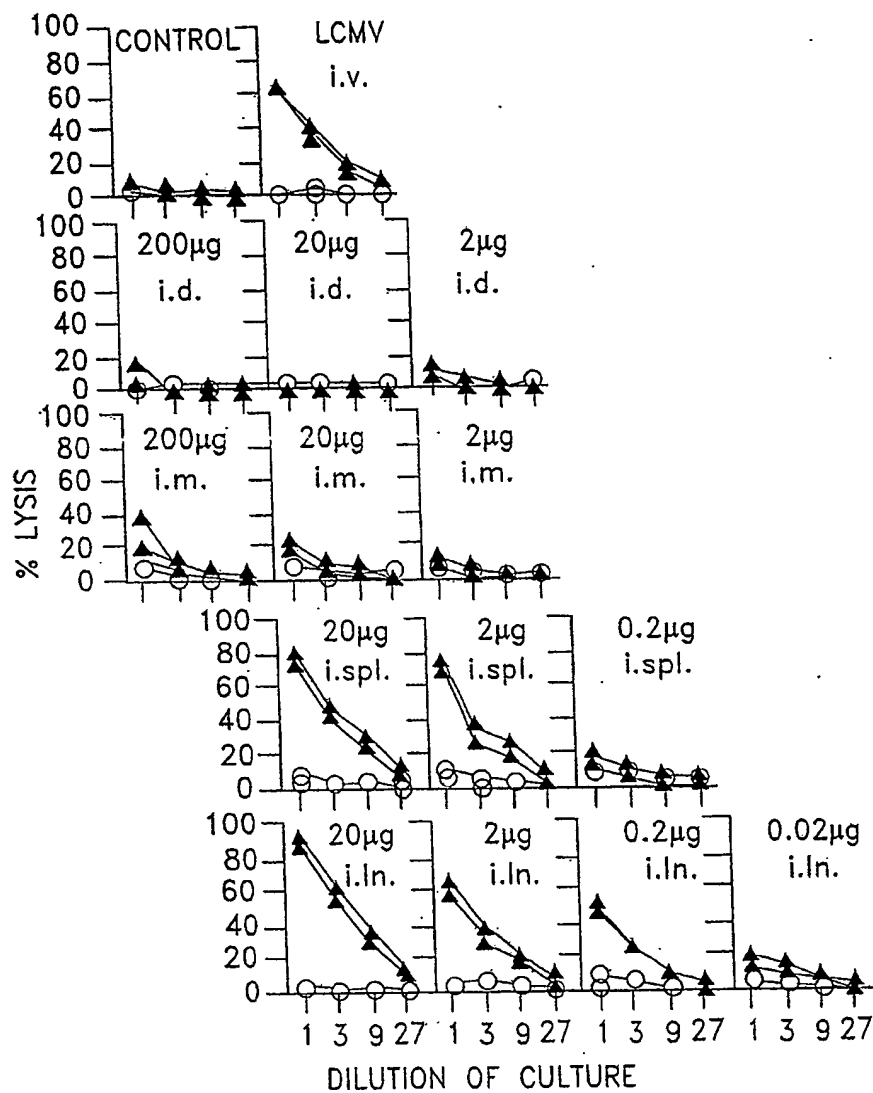


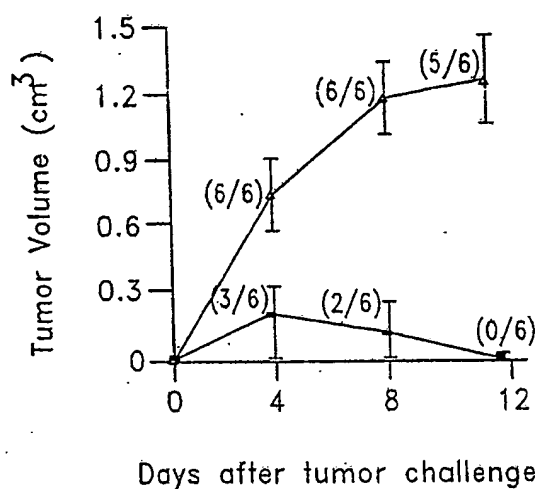
FIG. 14
Comparison of Peptides Binding Affinity
to HLA A2 by Binding Assay





Graphs show lysis of unpulsed EL4 cells (open circles) and EL4 cells pulsed with gp33 peptide (solid triangles). Symbols represent individual mice and one of three similar experiments is shown.

FIG. 15



Mean tumor volumes \pm 1SD are shown for mice immunized with pEFGPL33A DNA (solid circles) or control pEGFP-N3 DNA (open triangles). Numbers in brackets indicate number of mice with tumors/total number of mice in group. One of two similar experiments is shown.

FIG. 16

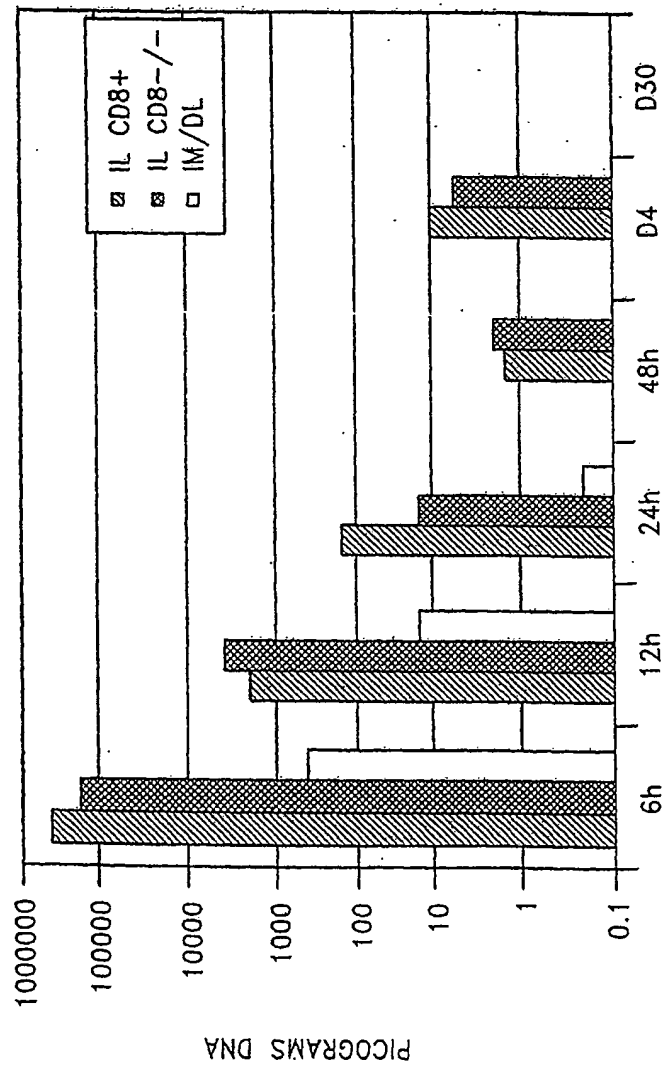


FIG. 17

Tyrosinase (171-203)

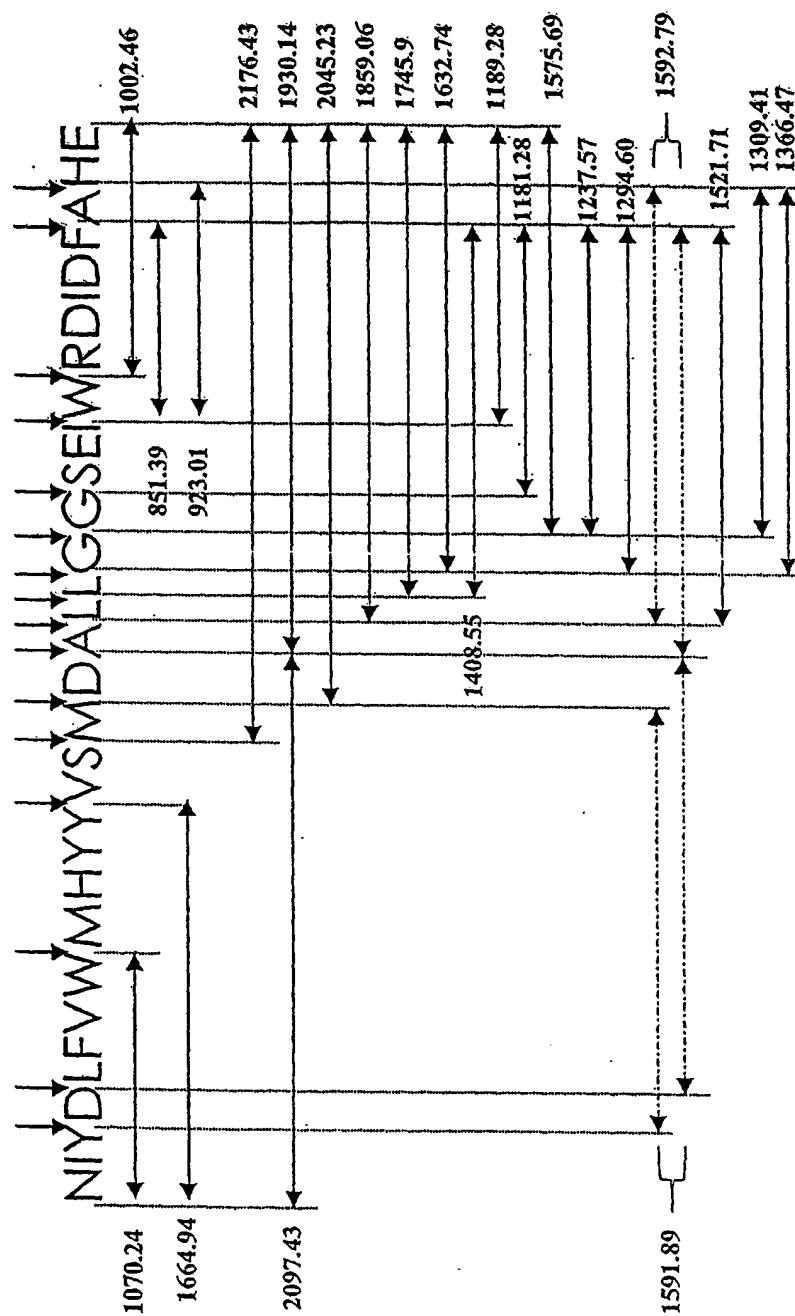


Figure 18

Tyr (401-427)

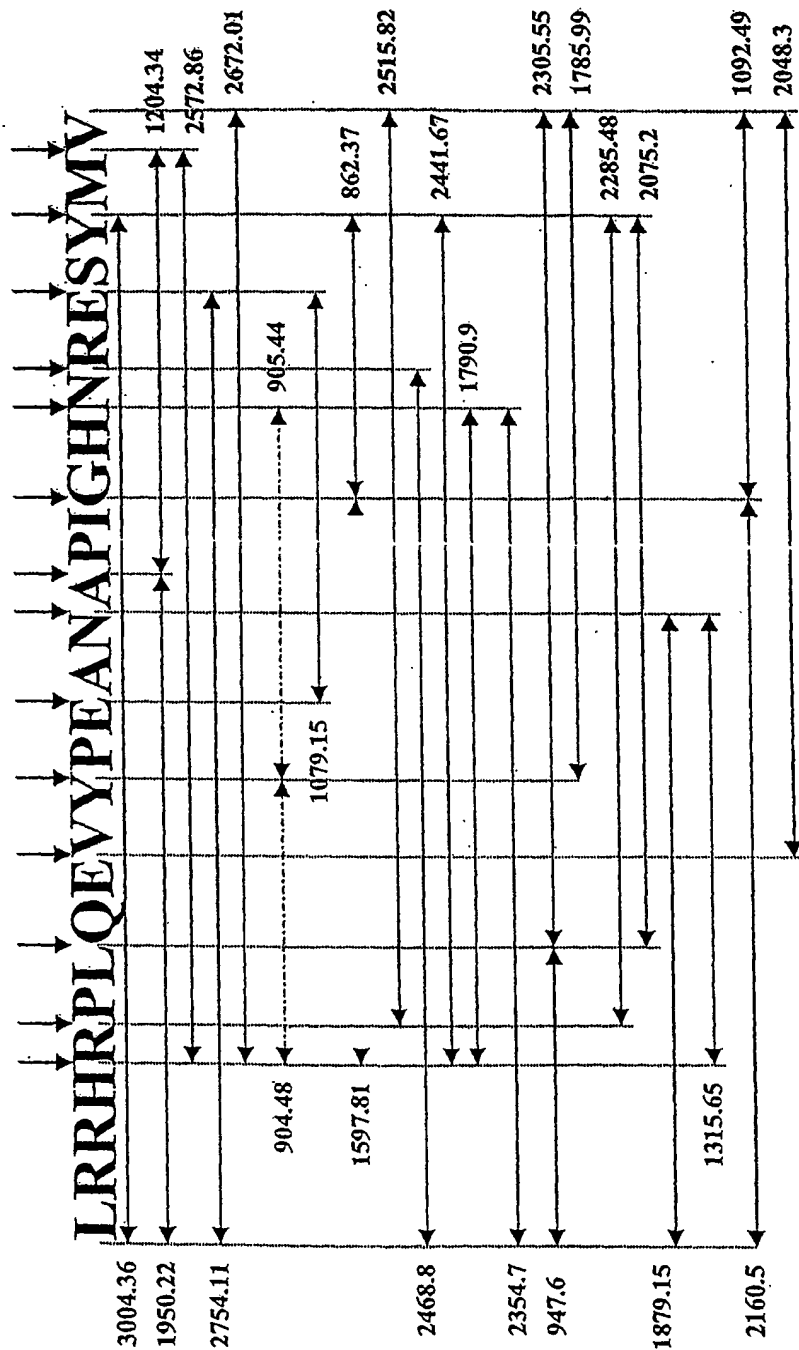


Figure 19

Tyrosinase (415-449)

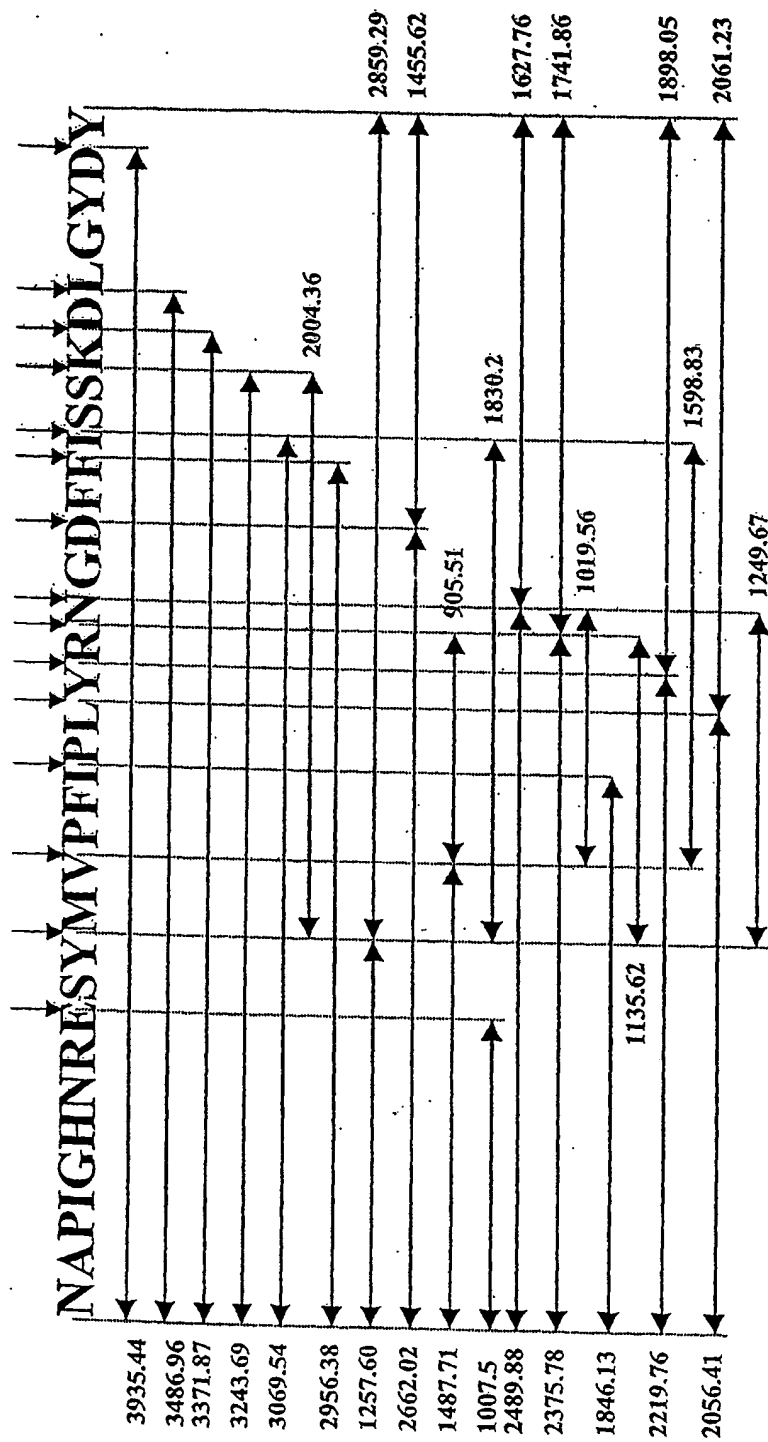


Figure 20

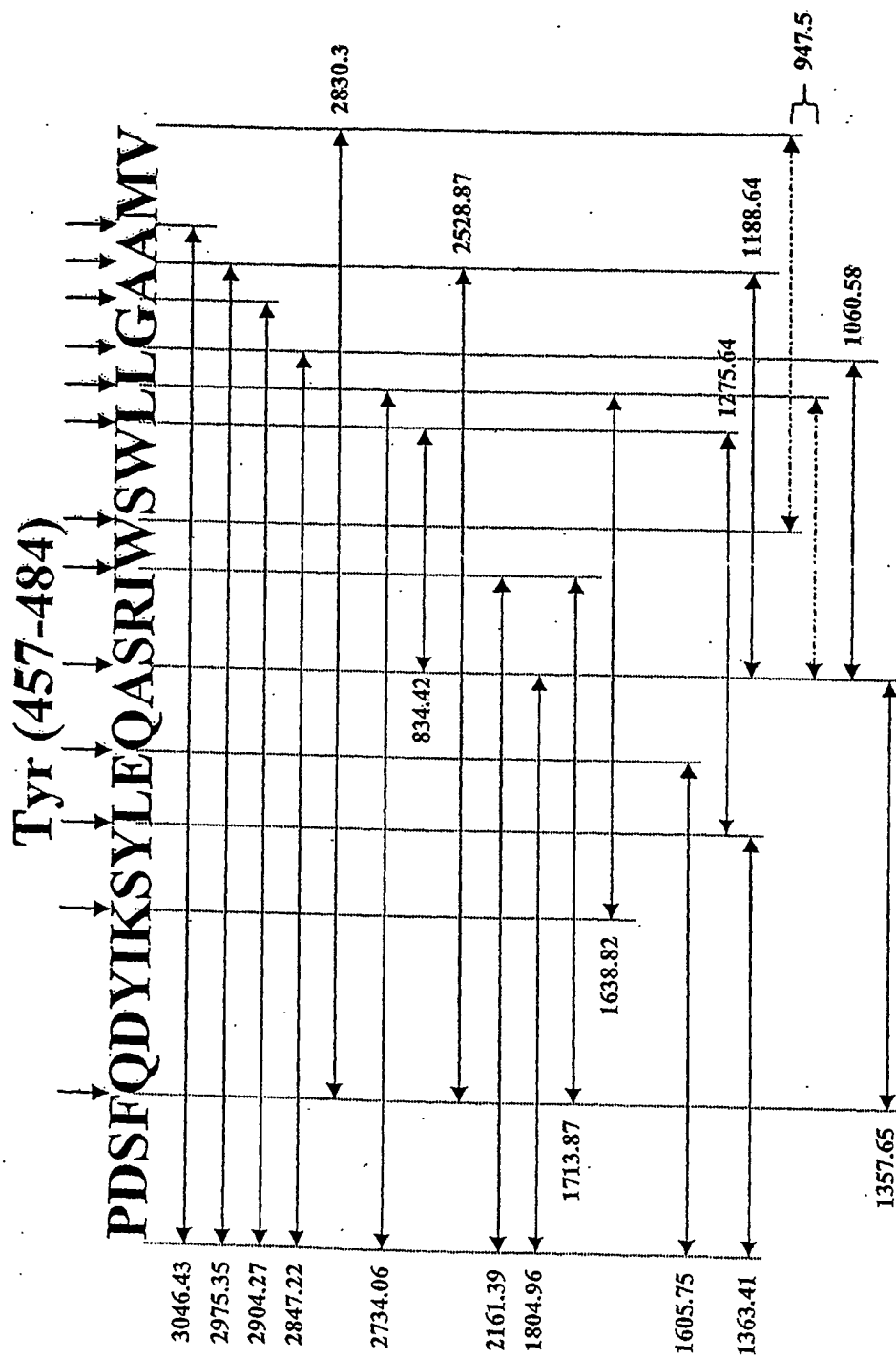


Figure 21

CEA 92-118

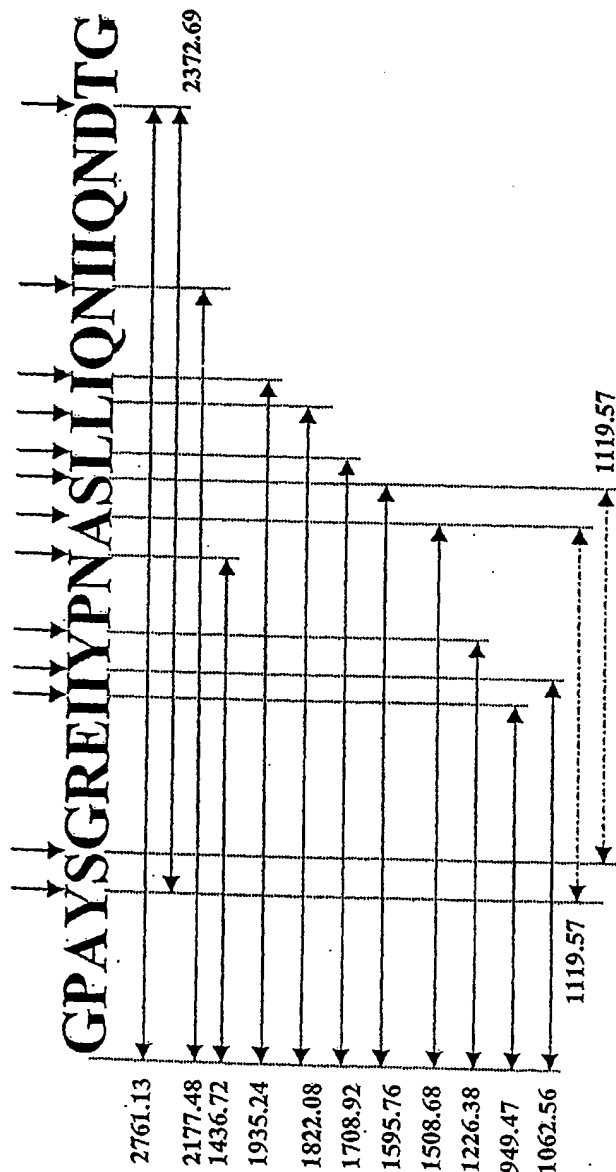


Figure 22

CEA 131-159

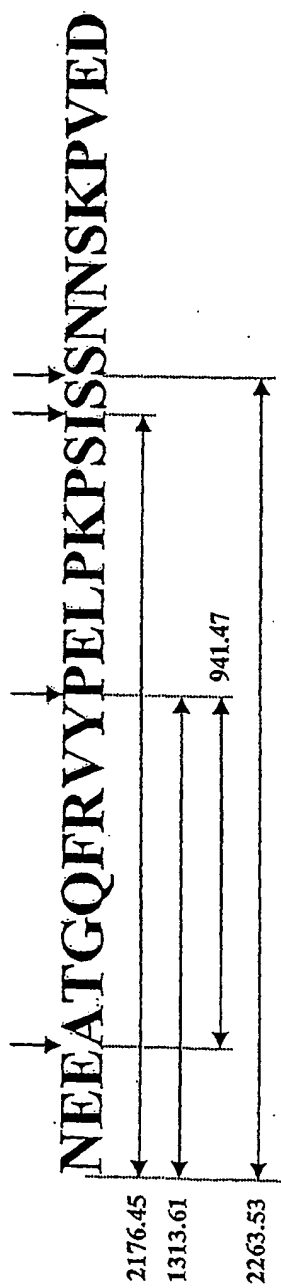


Figure 23

CEA 225-251

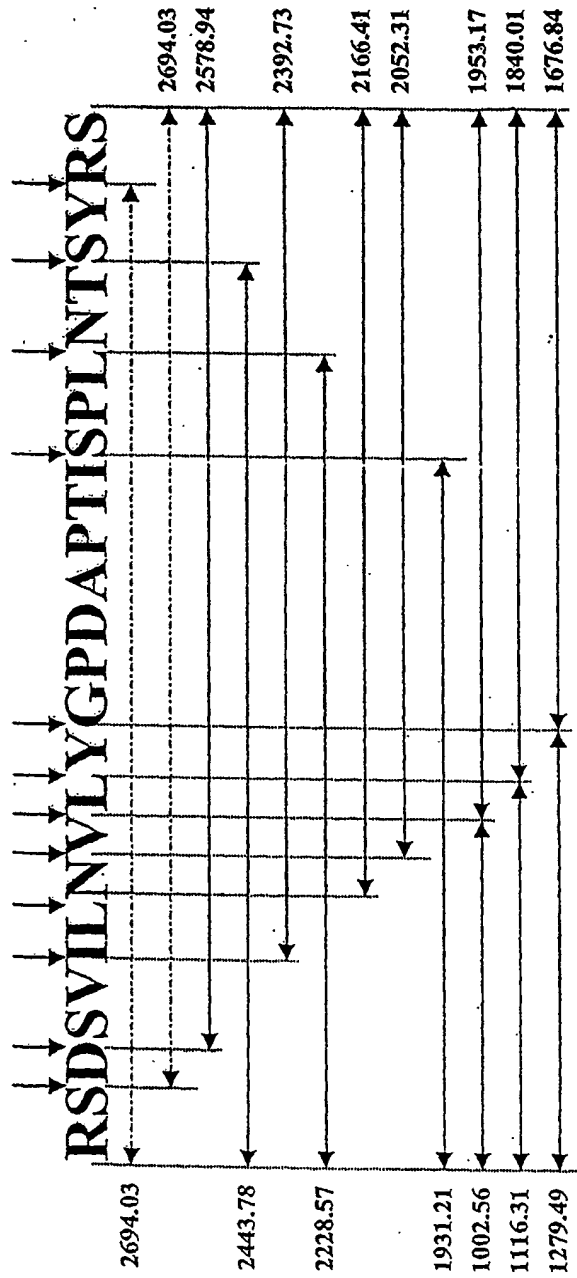


Figure 24

CEA 239-270

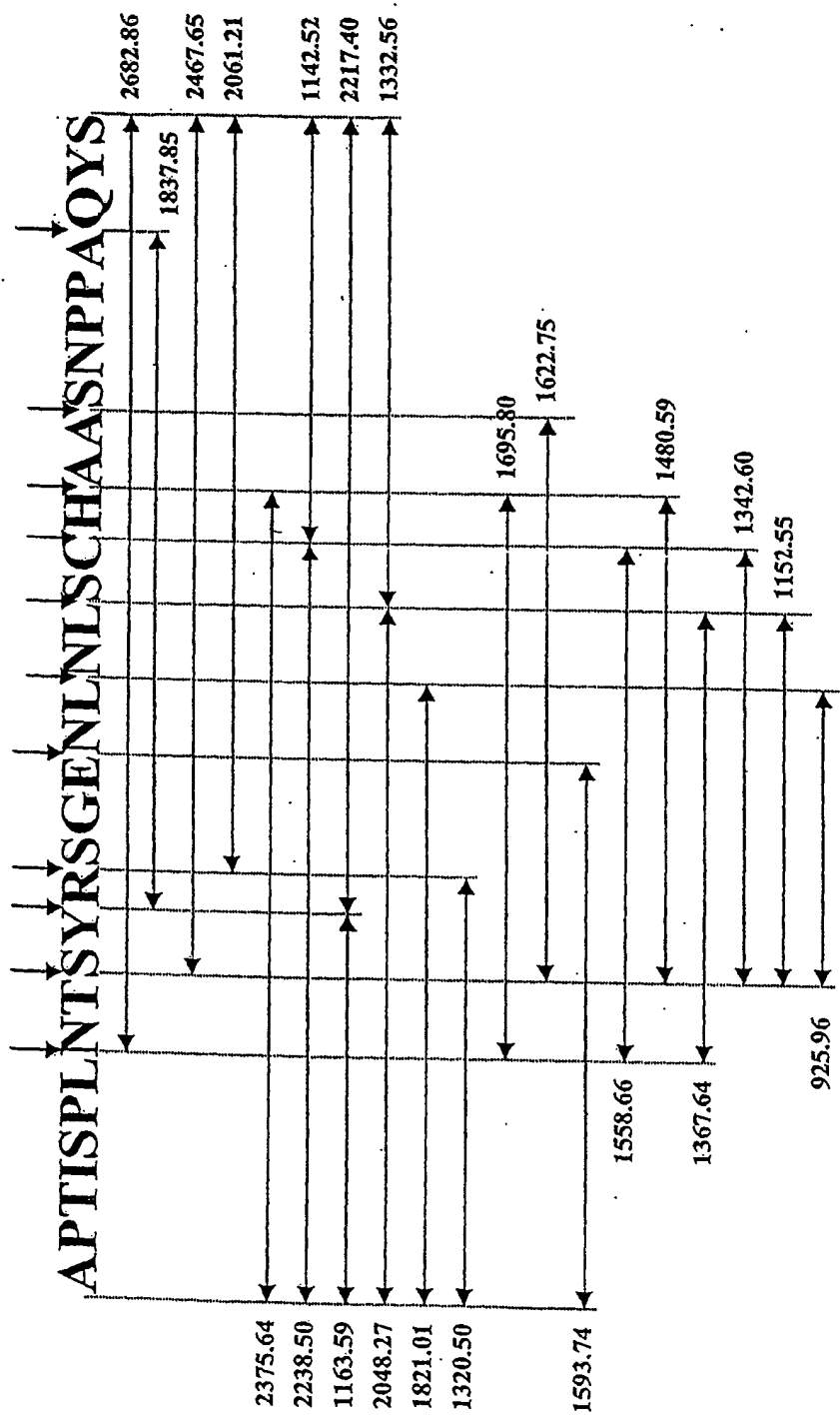


Figure 25

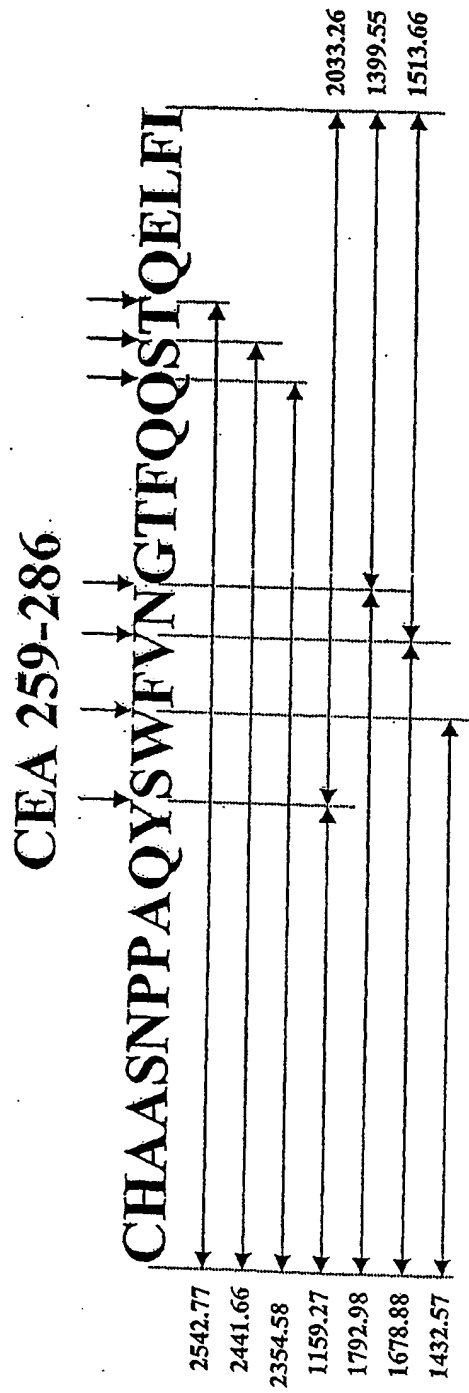


Figure 26

CEA 309-336

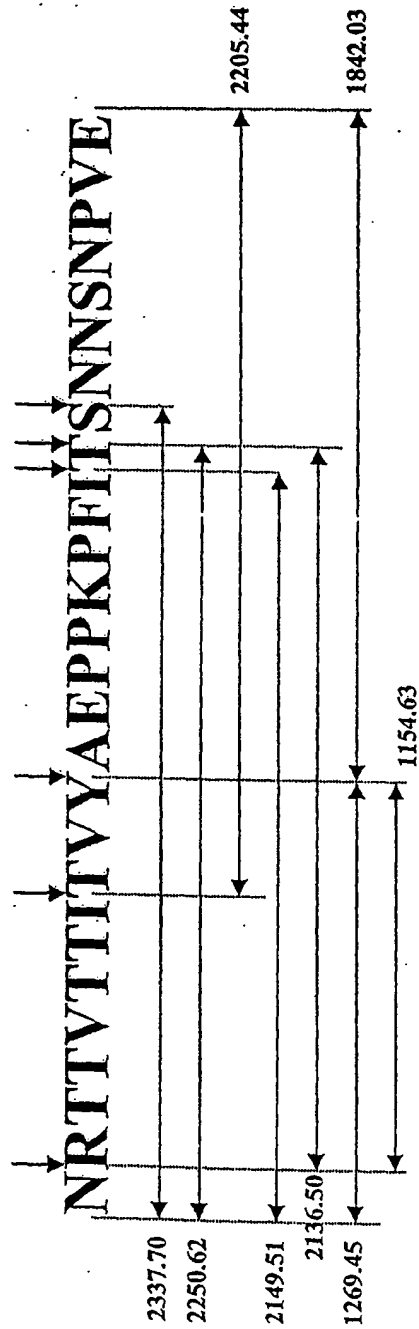


Figure 27

CEA 381-408

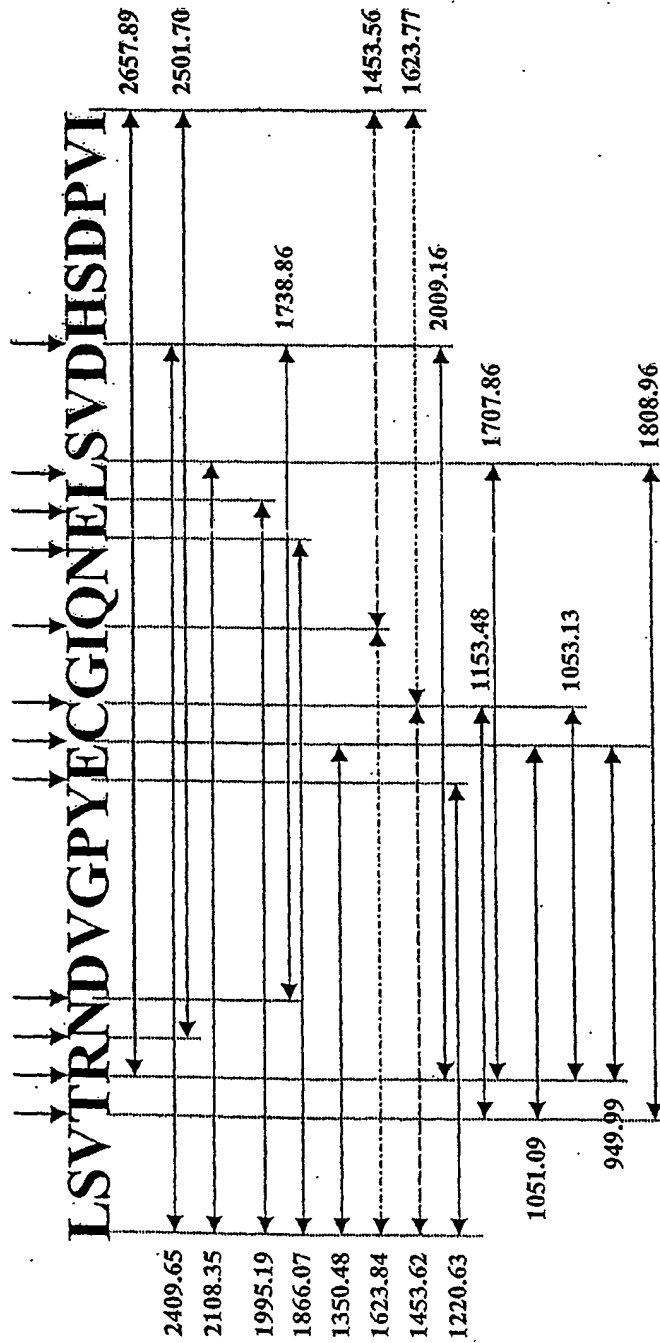


Figure 28

CEA 403-429

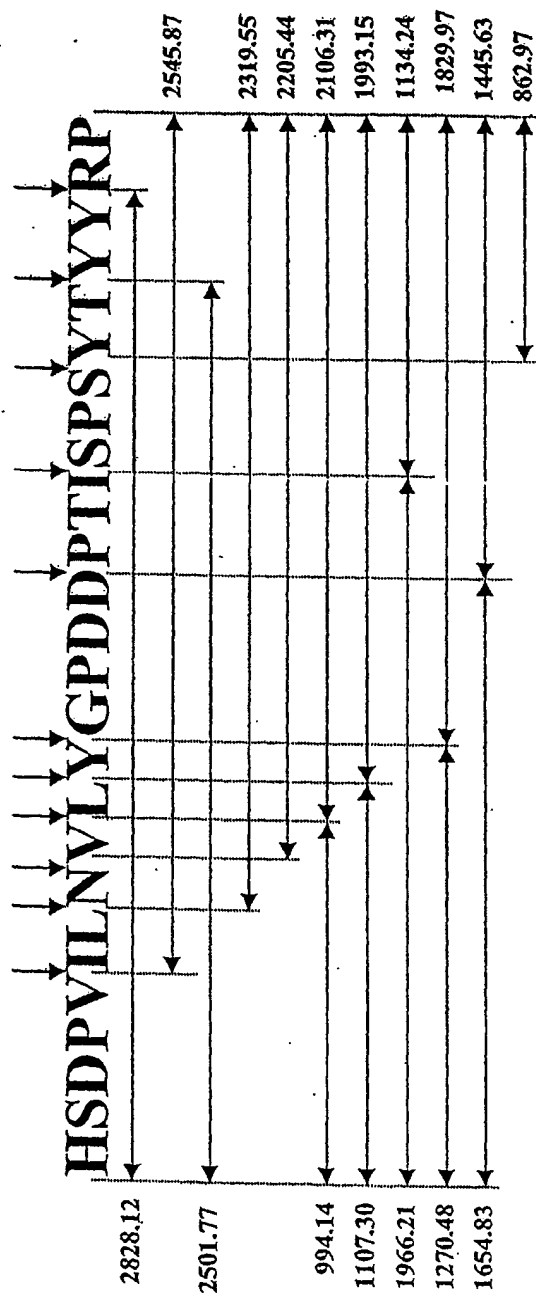


Figure 29

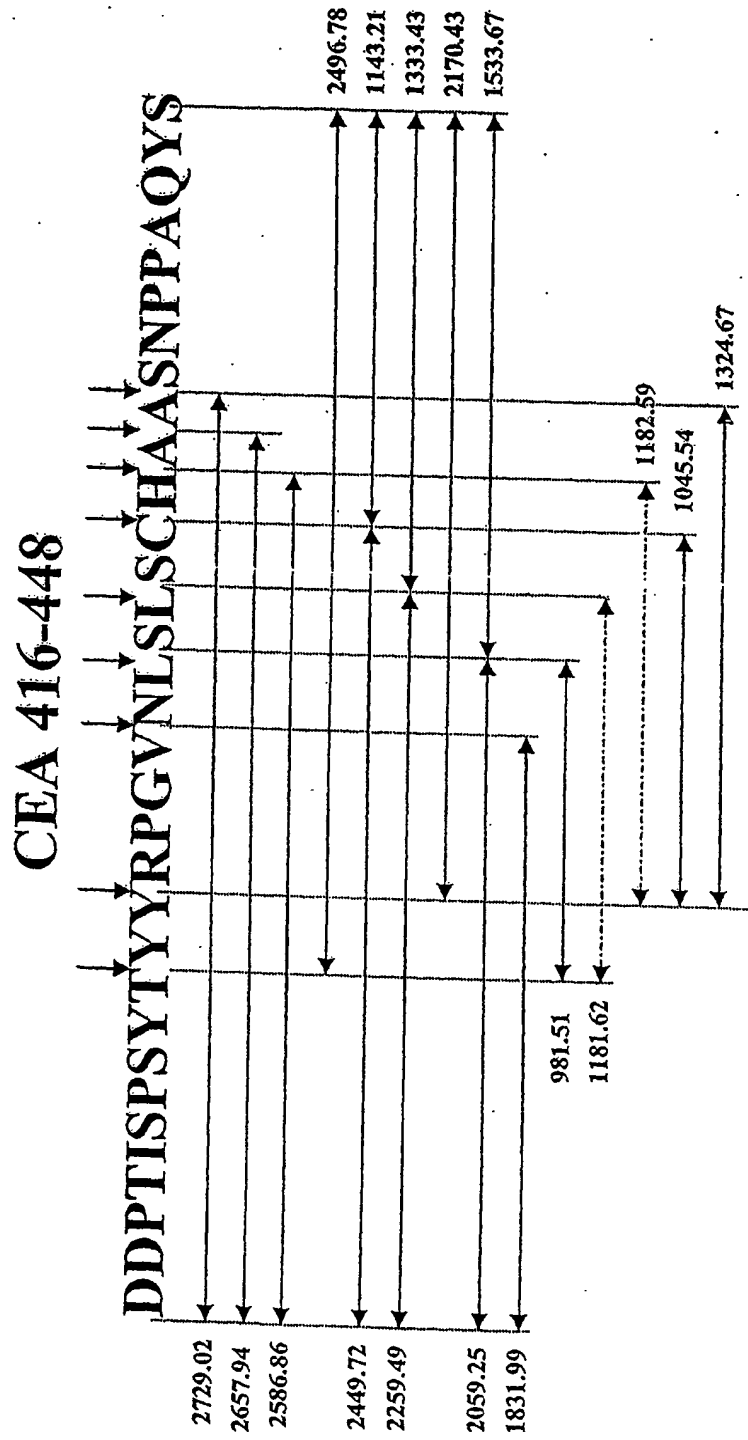


Figure 30

CEA 437-464

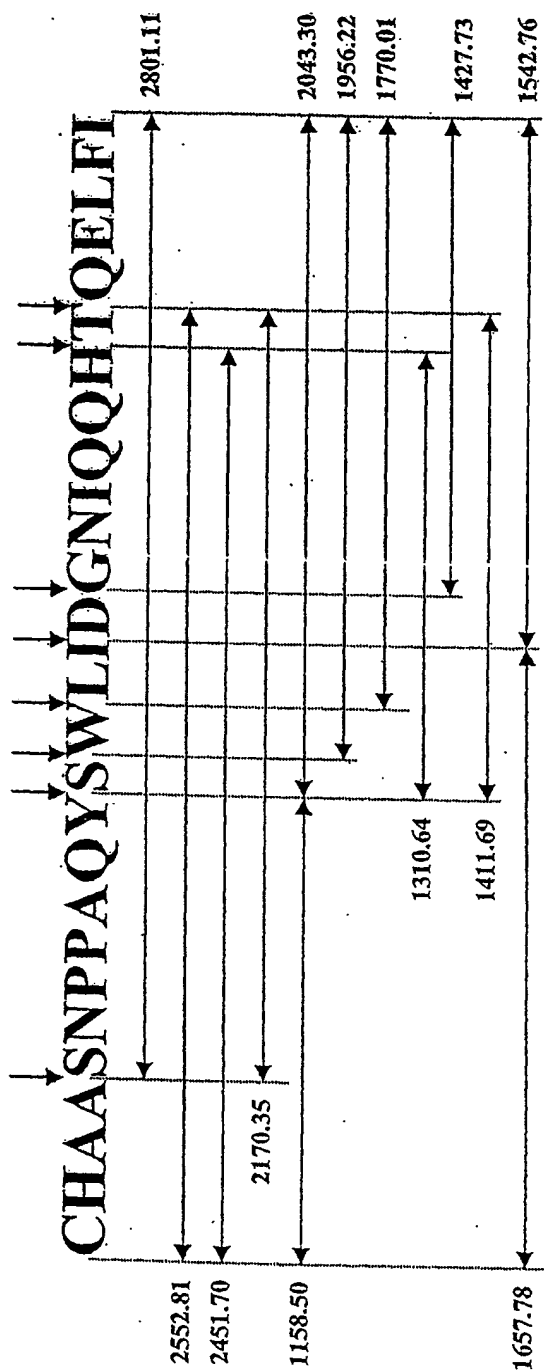


Figure 31

CEA 581-607

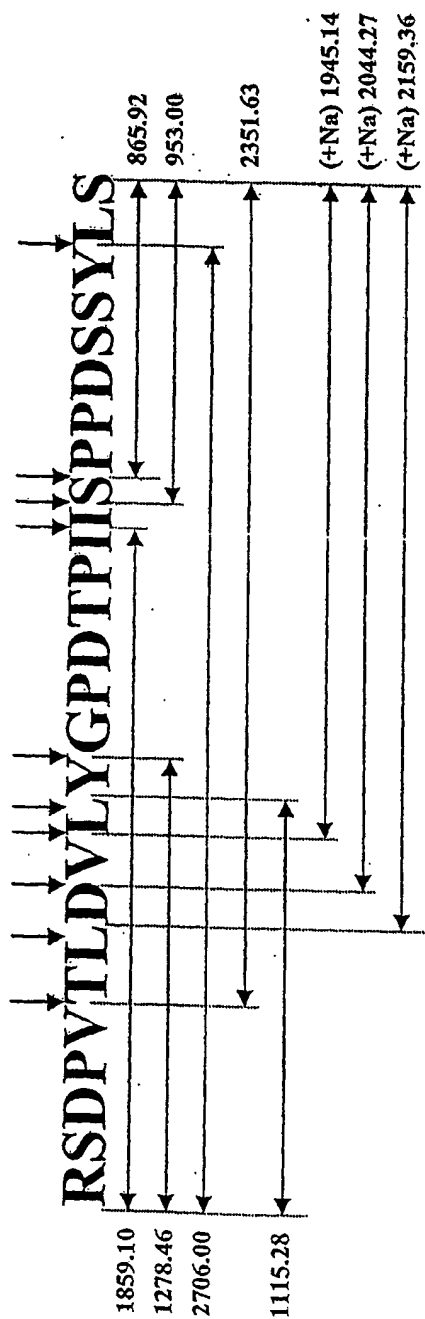


Figure 32

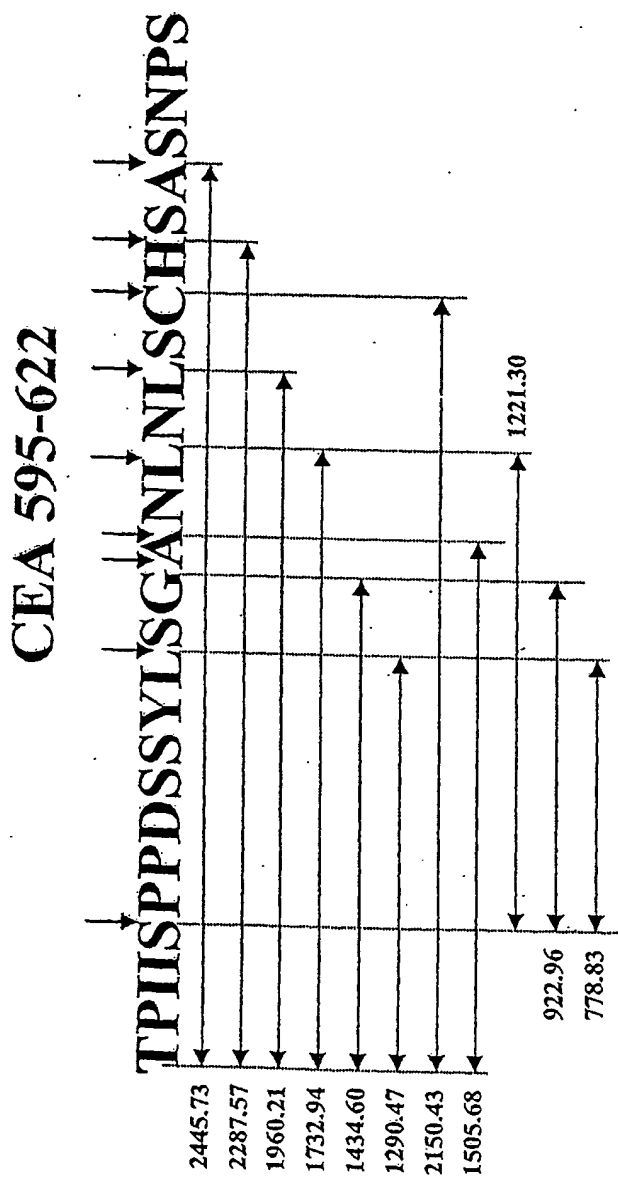


Figure 33

CEA 615-64I

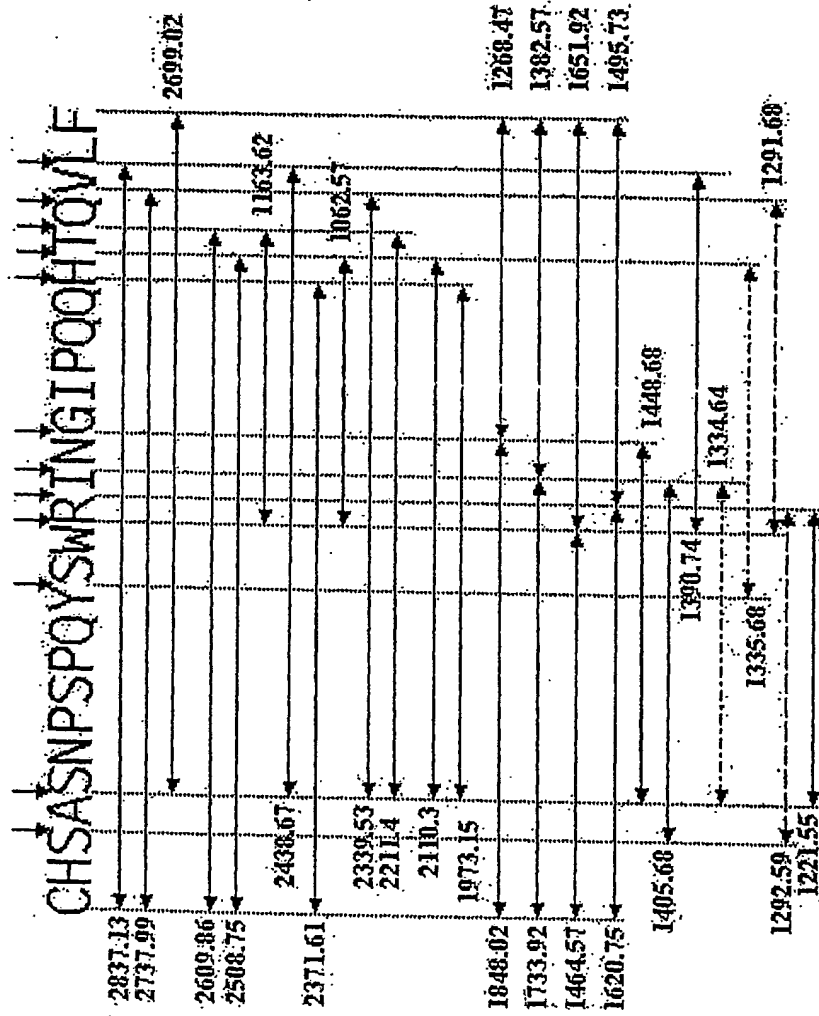


Figure 34

CEA 643-677

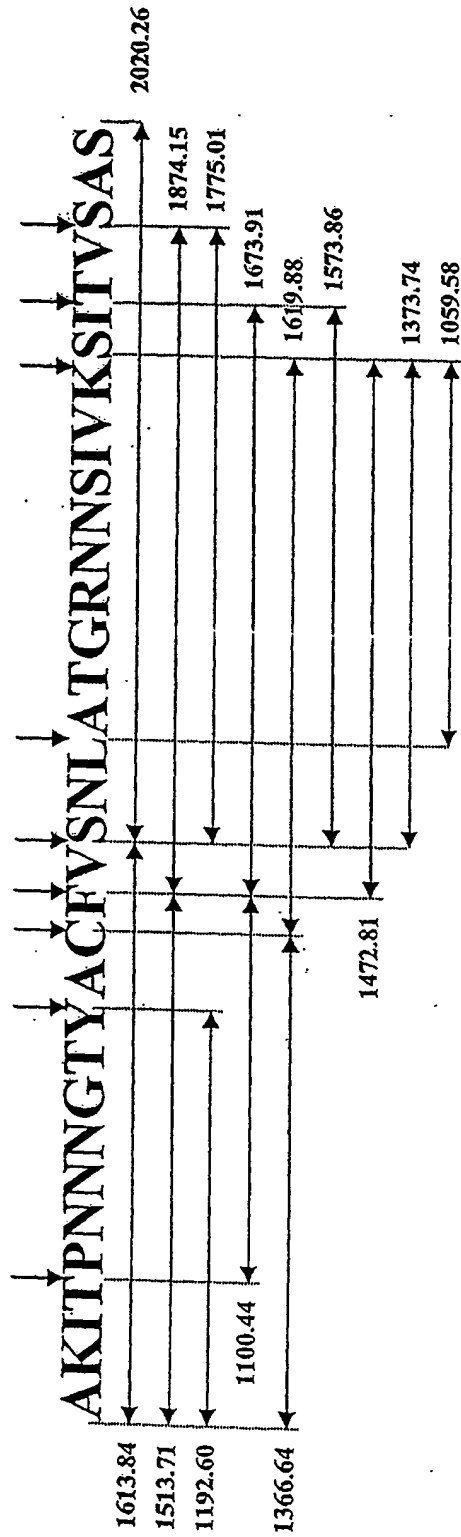


Figure 35

GAGE-1 (6-32) 30 min

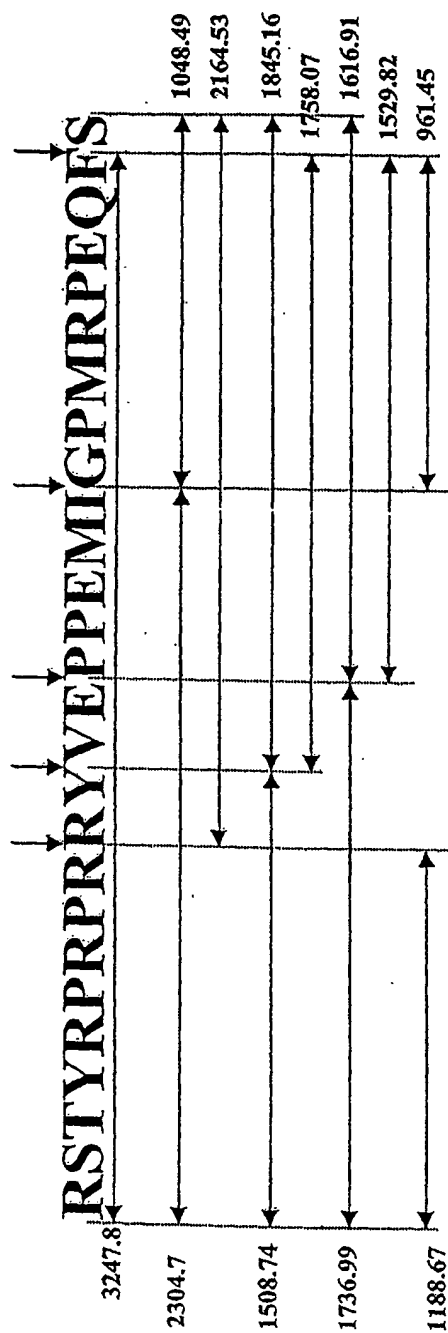


Figure 36

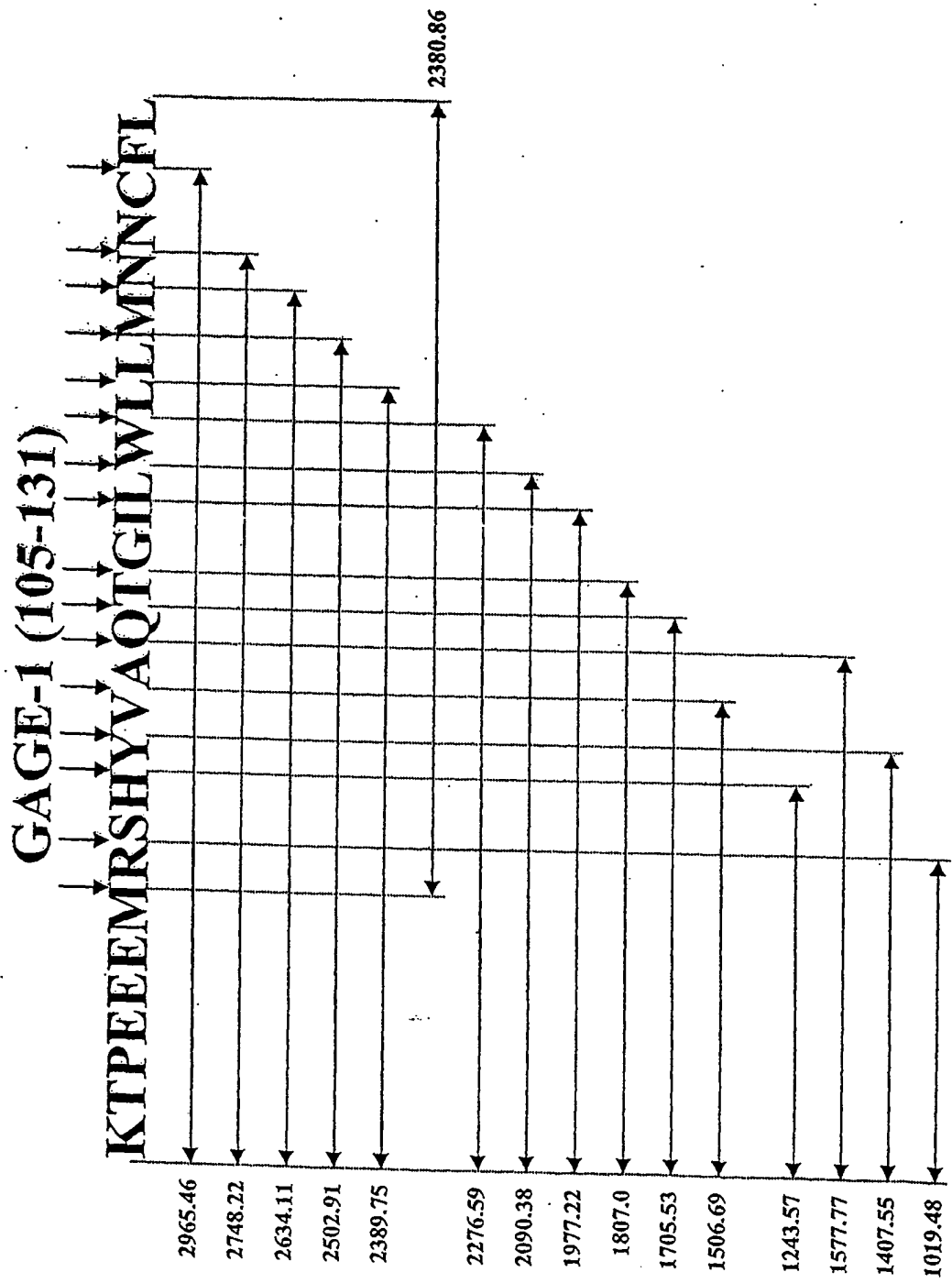


Figure 37

GAGE-1 (112-137)

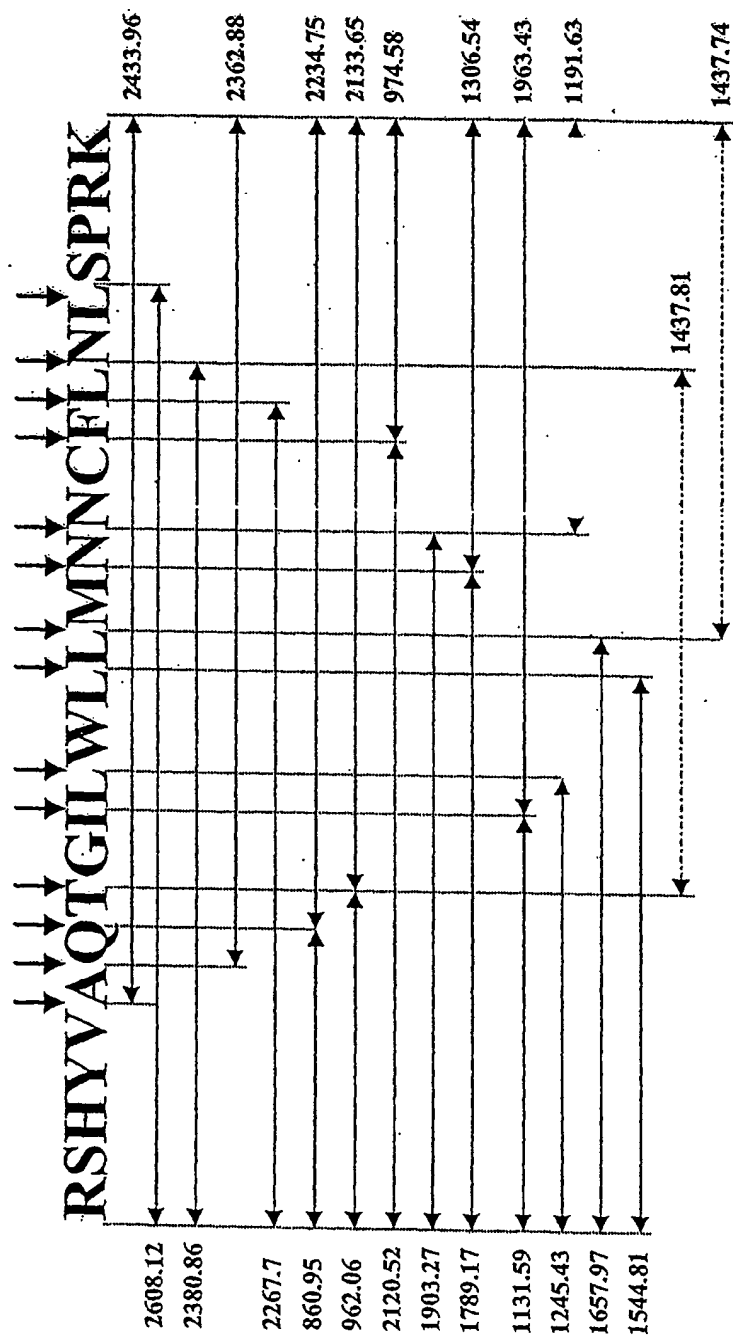


Figure 38

MAGE-1 (51-77)

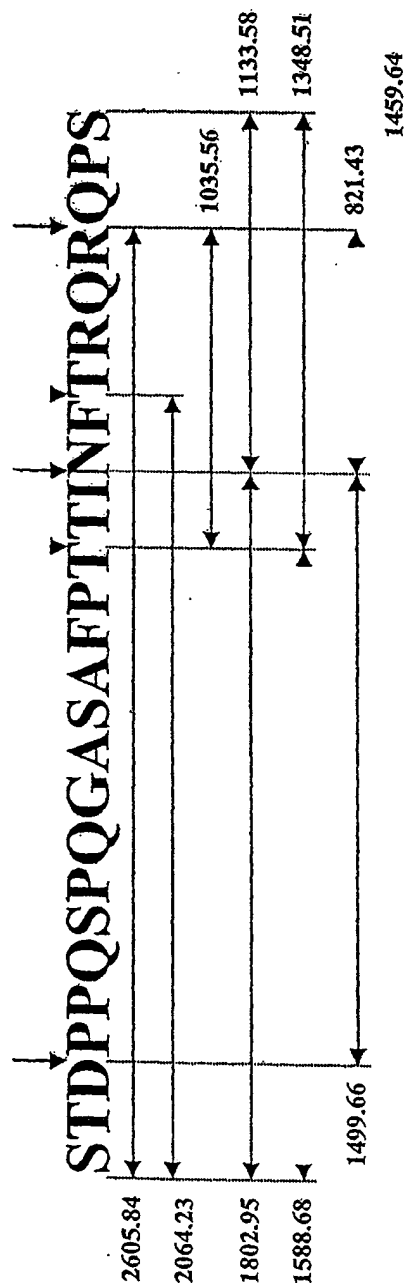


Figure 39

MAGE-1 (126-153)

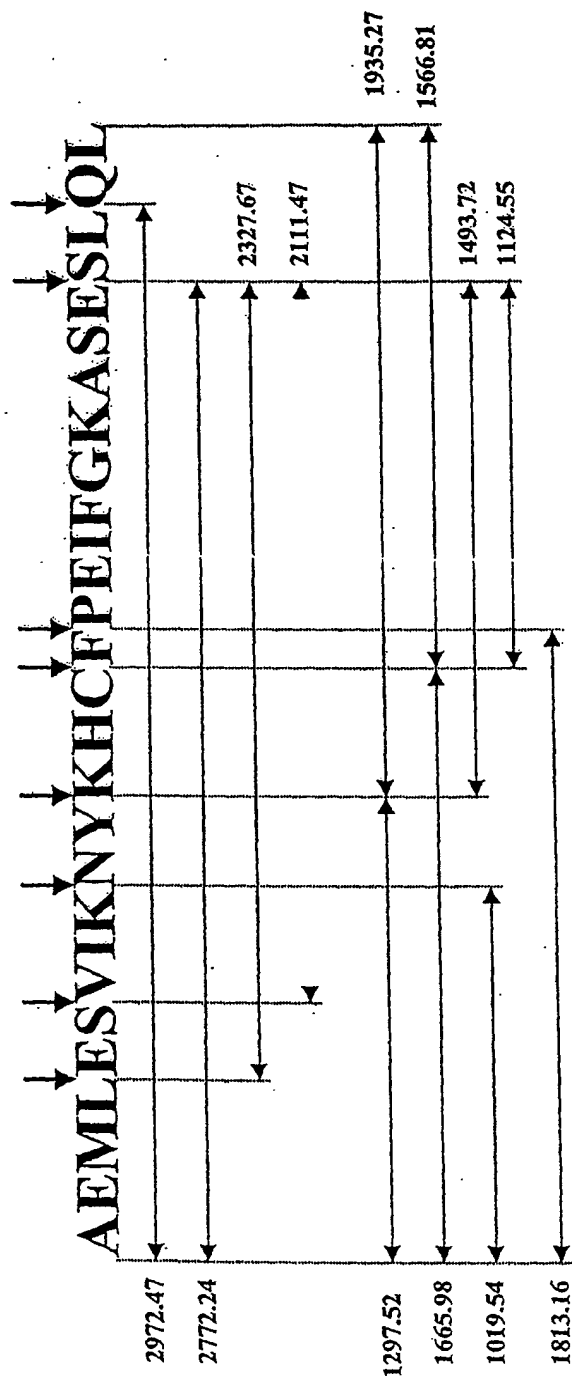


Figure 40

MAGE-2 (272-299)

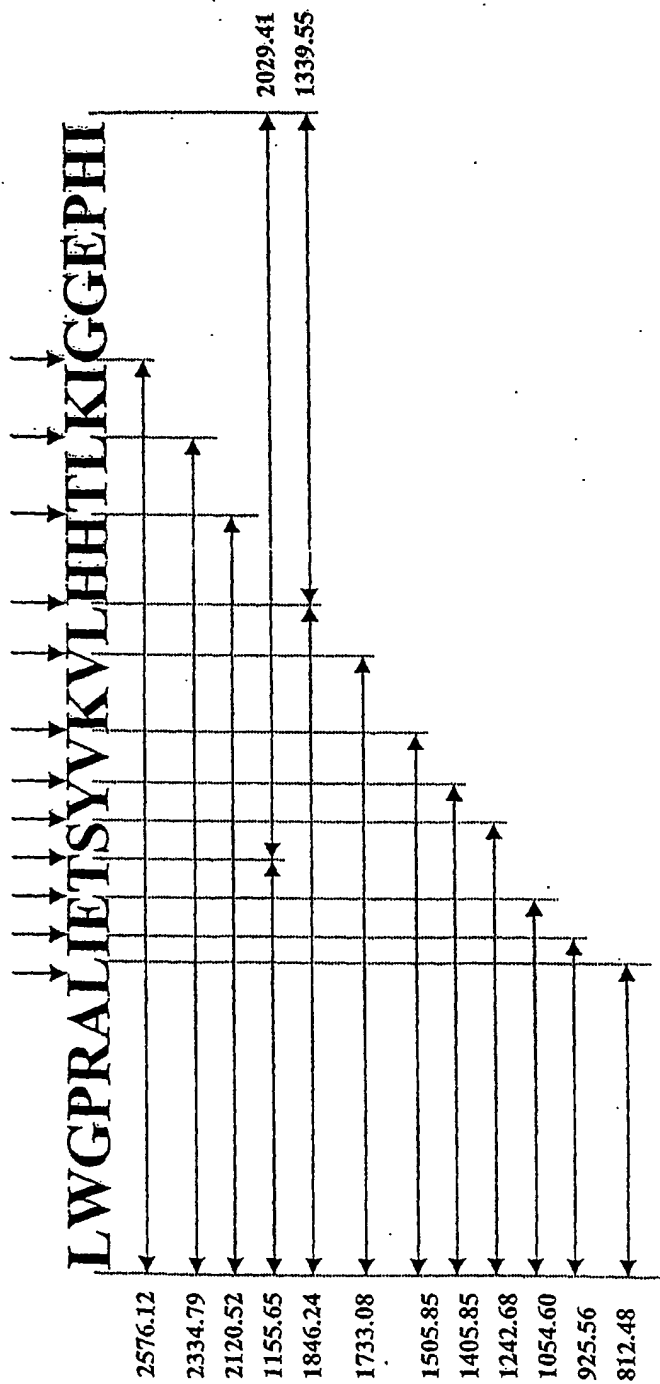


Figure 41

MAGE-2 (287-314)

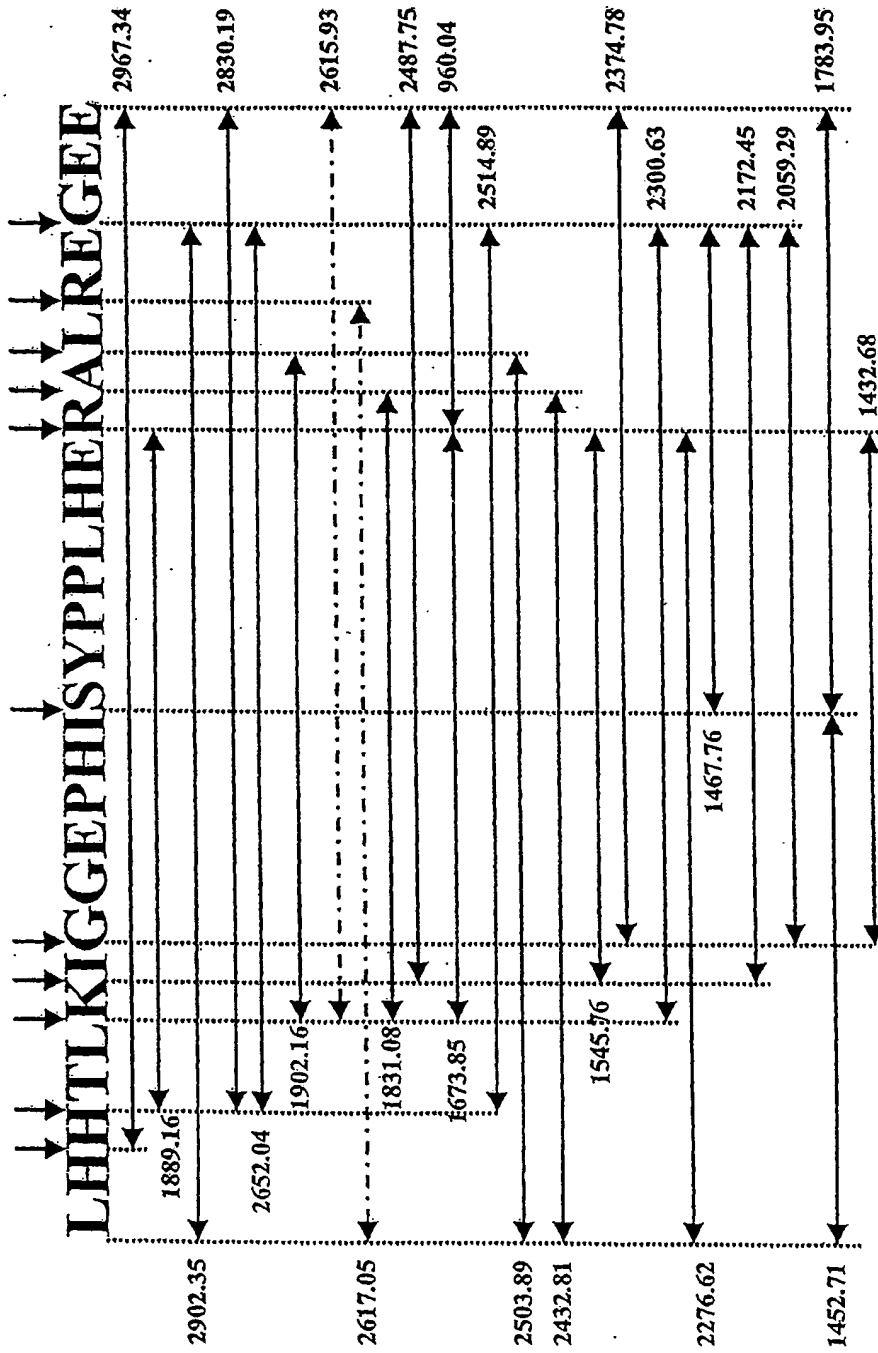


Figure 42

MAGE-3 (287-314)

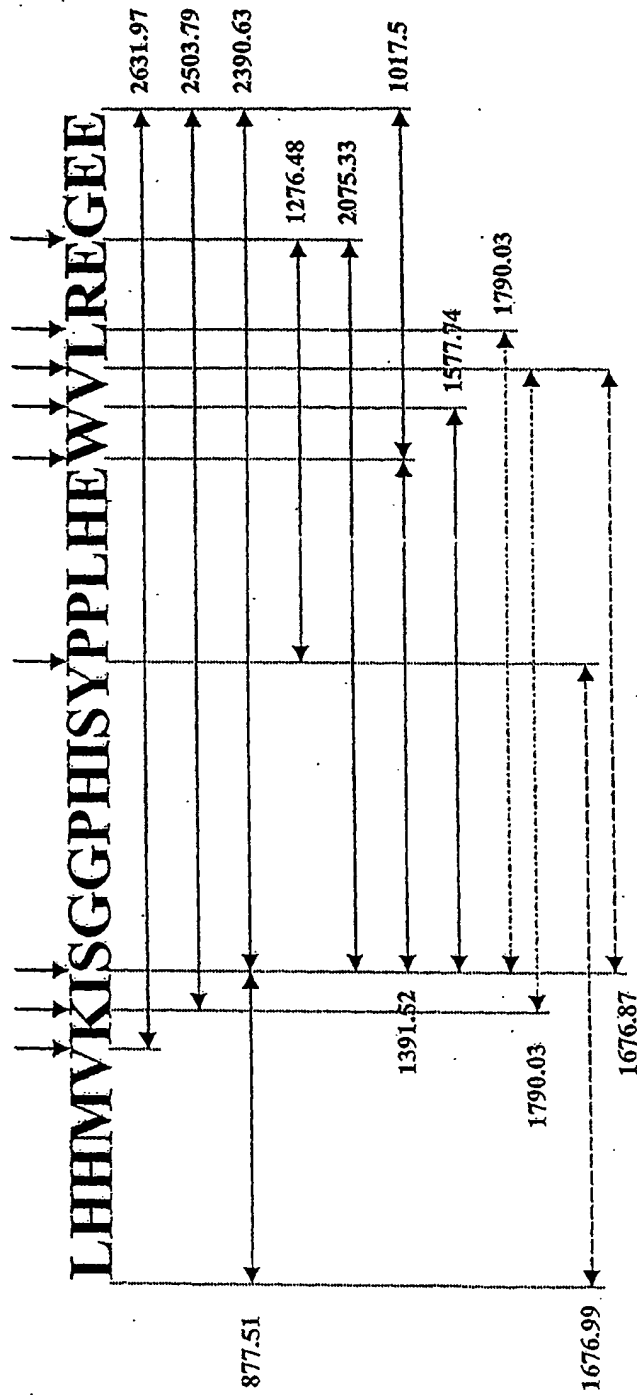


Figure 43

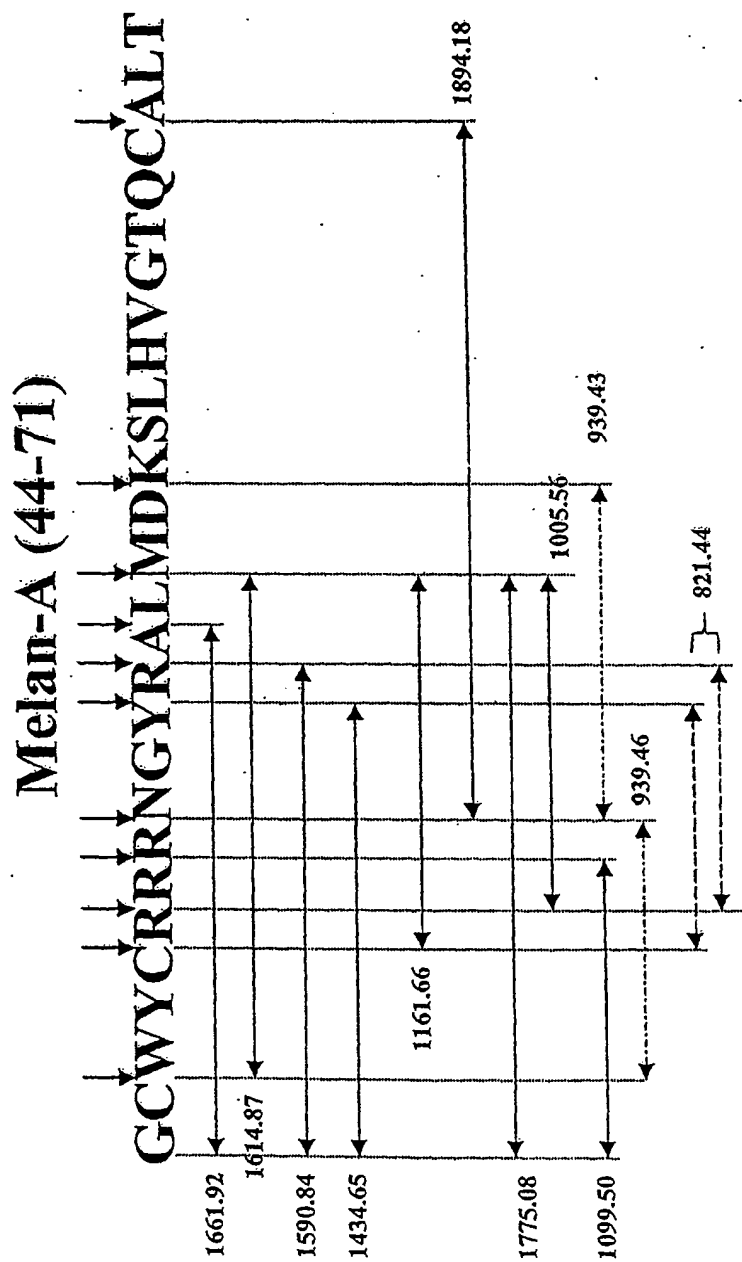


Figure 44

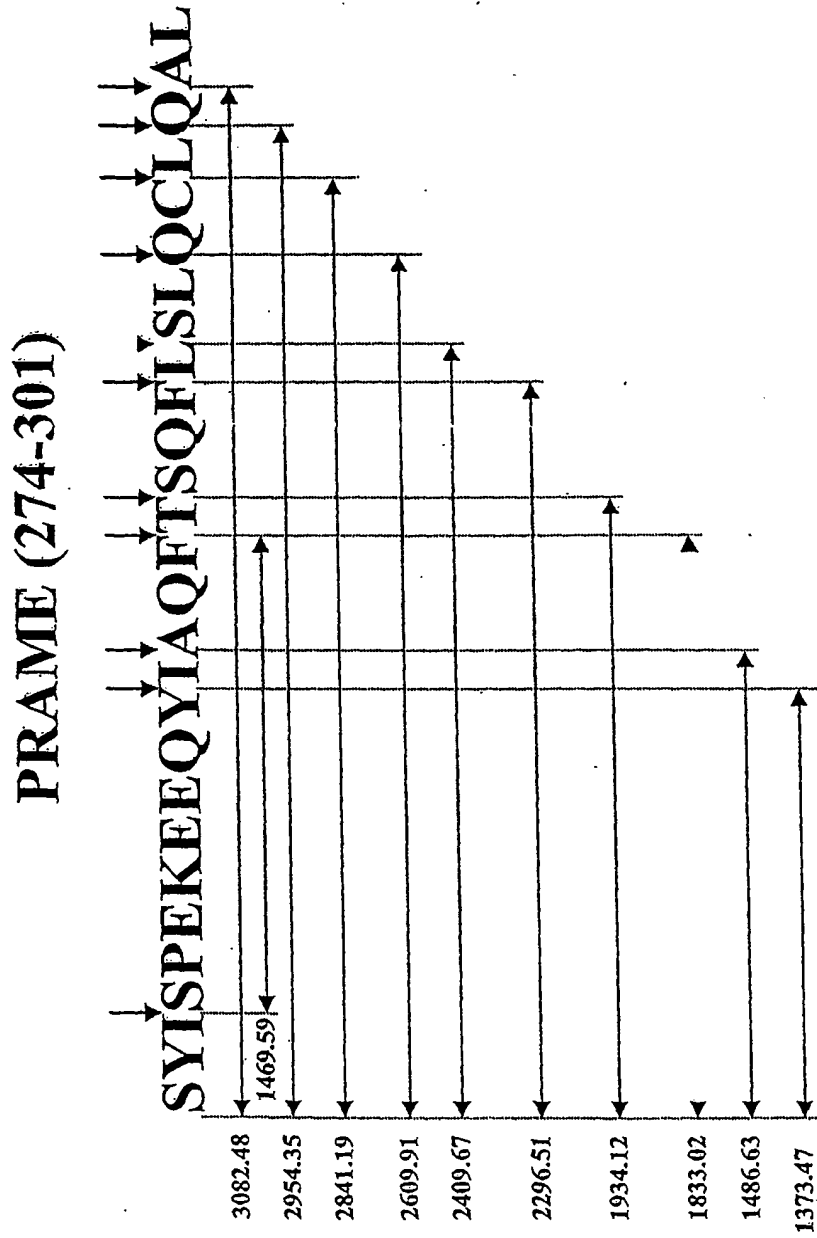


Figure 45

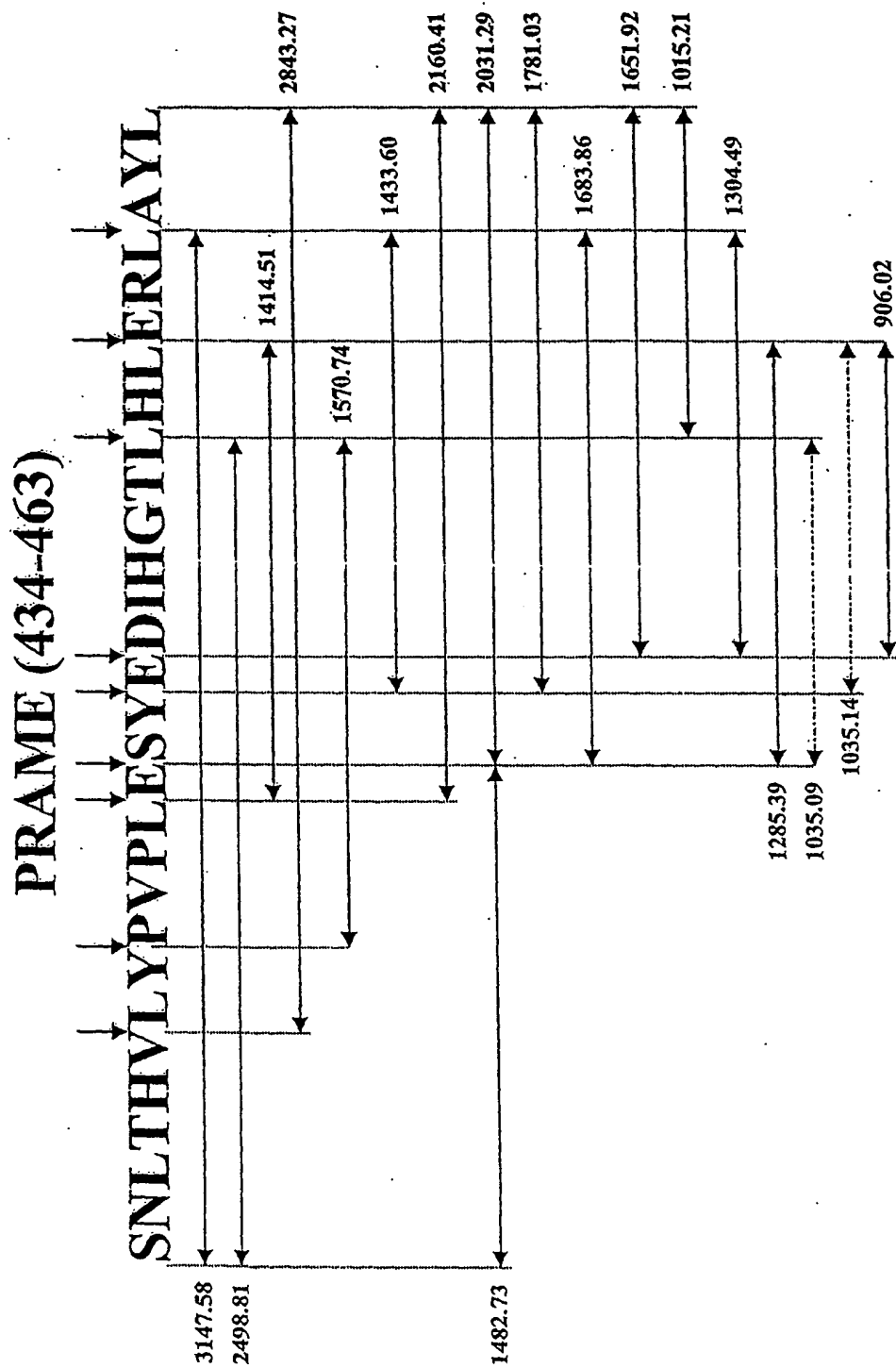


Figure 46

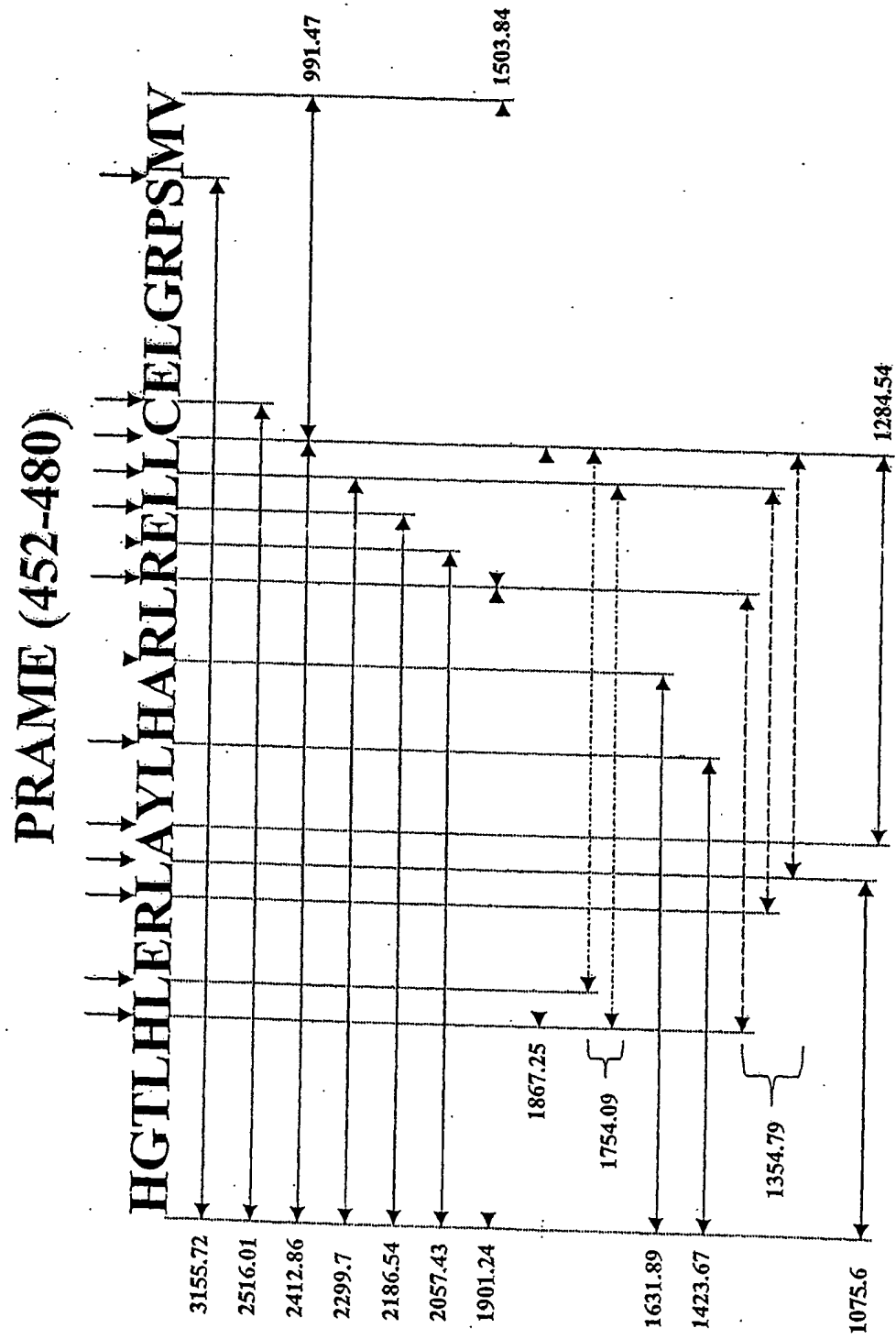


Figure 47

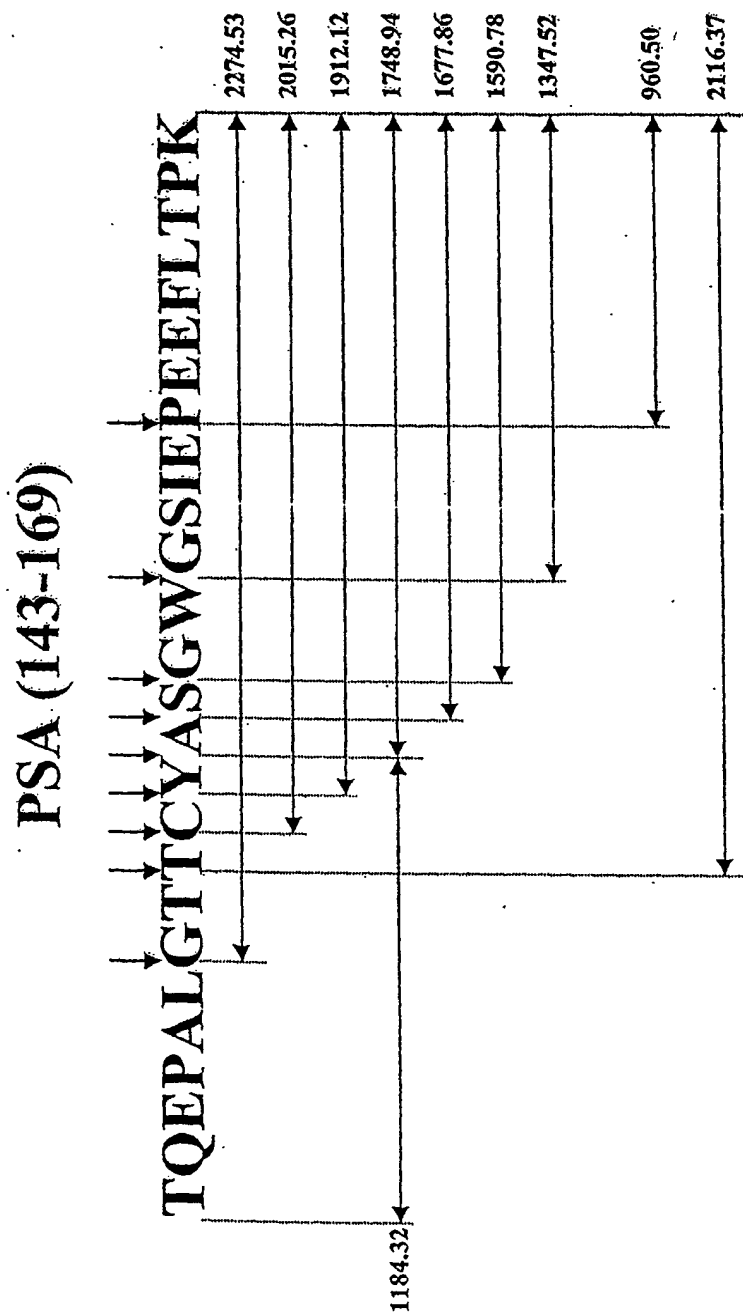


Figure 48

PSA 156-188

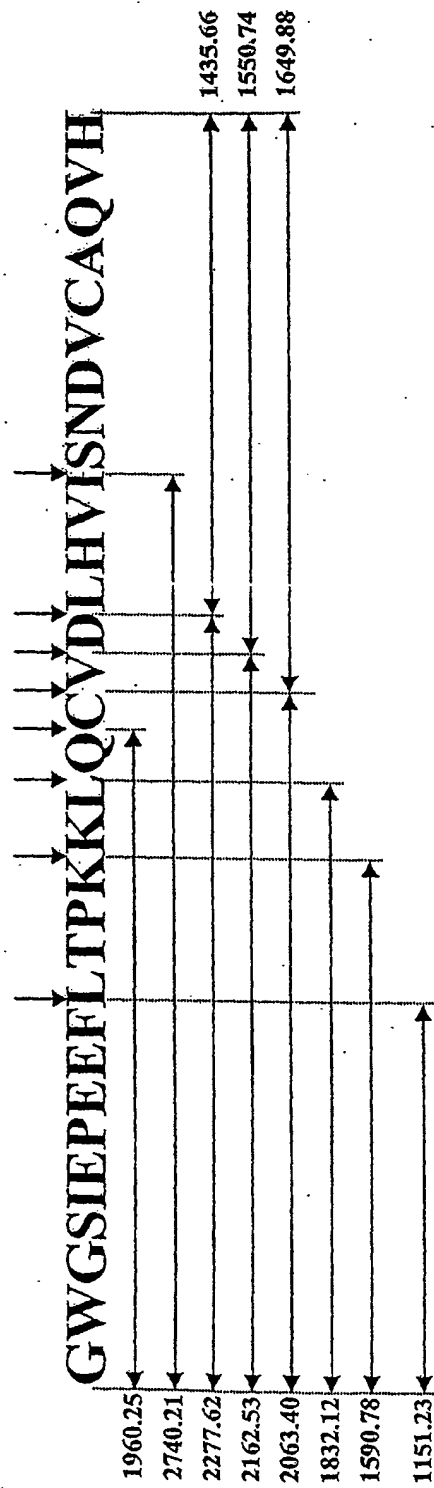


Figure 49

PSCA 67-94

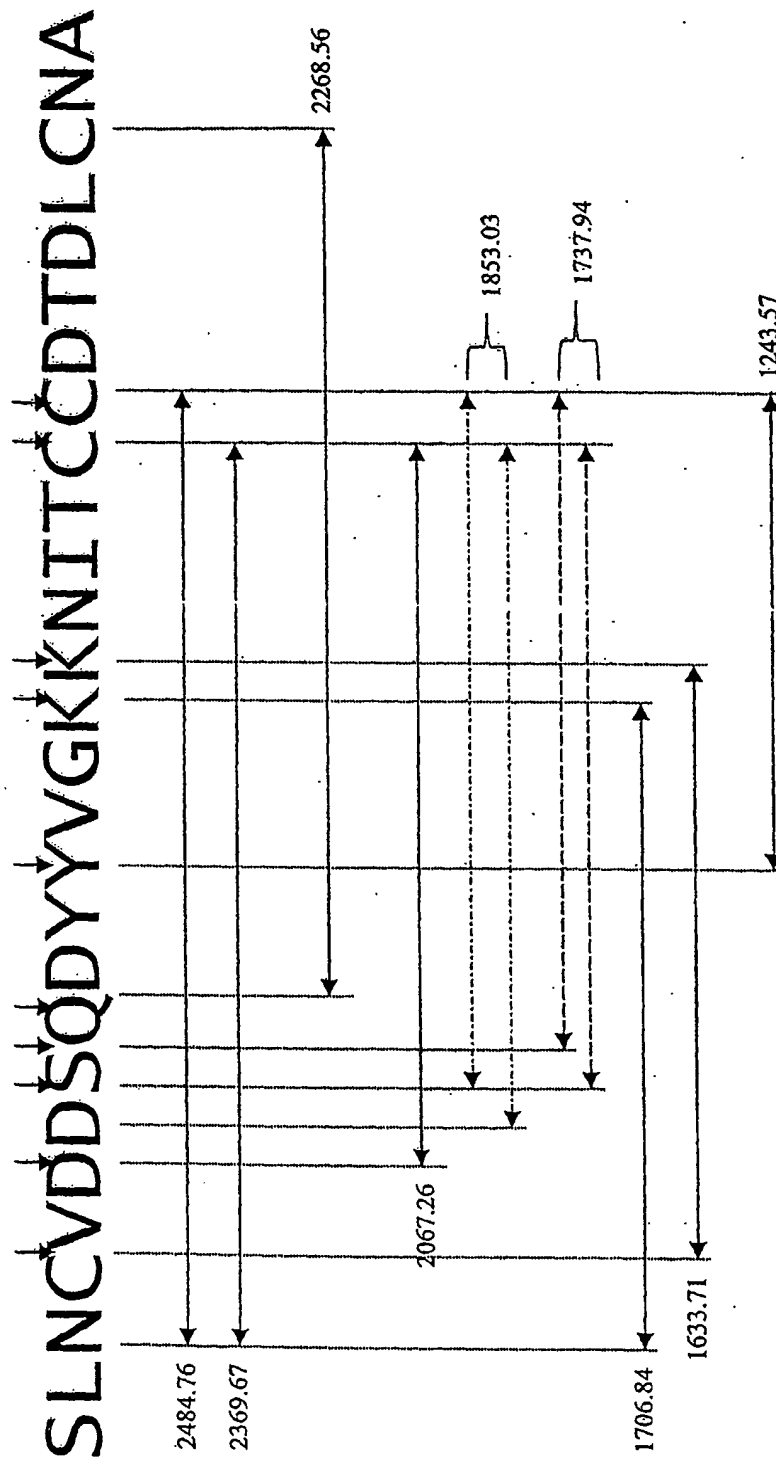


Figure 50

PSMA (378-405)

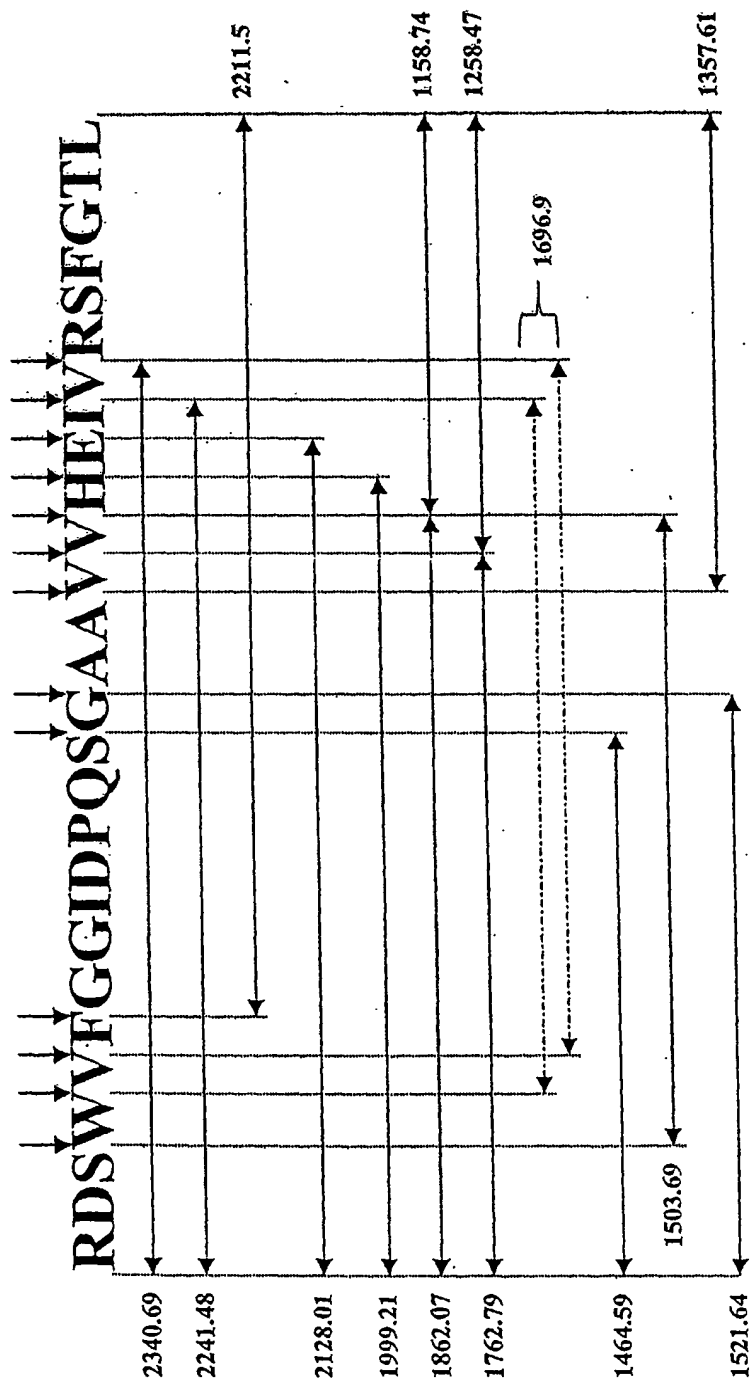


Figure 51

PSMA (597-623)

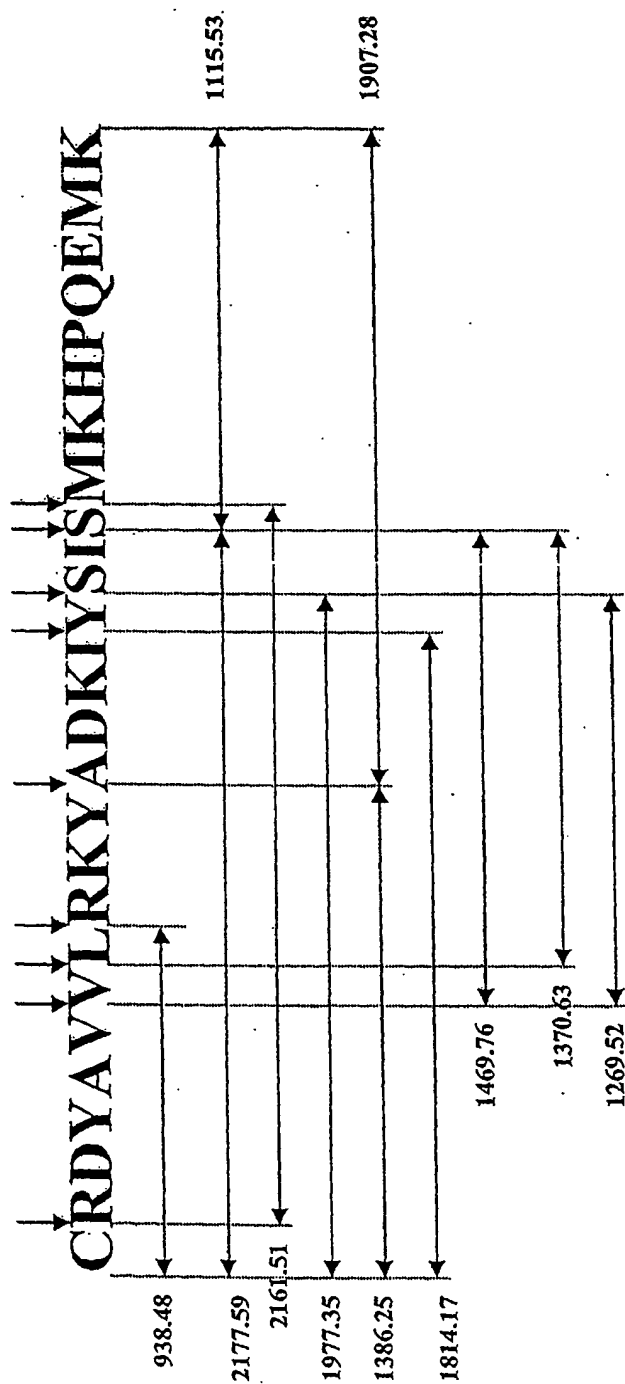


Figure 52

PSMA (615-642)

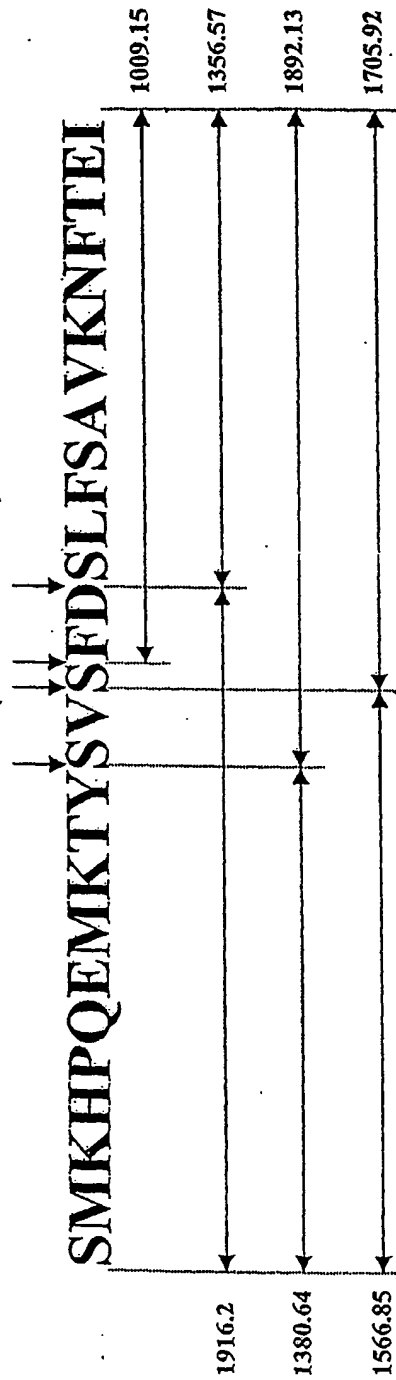


Figure 53

SCP-1 (57-86)

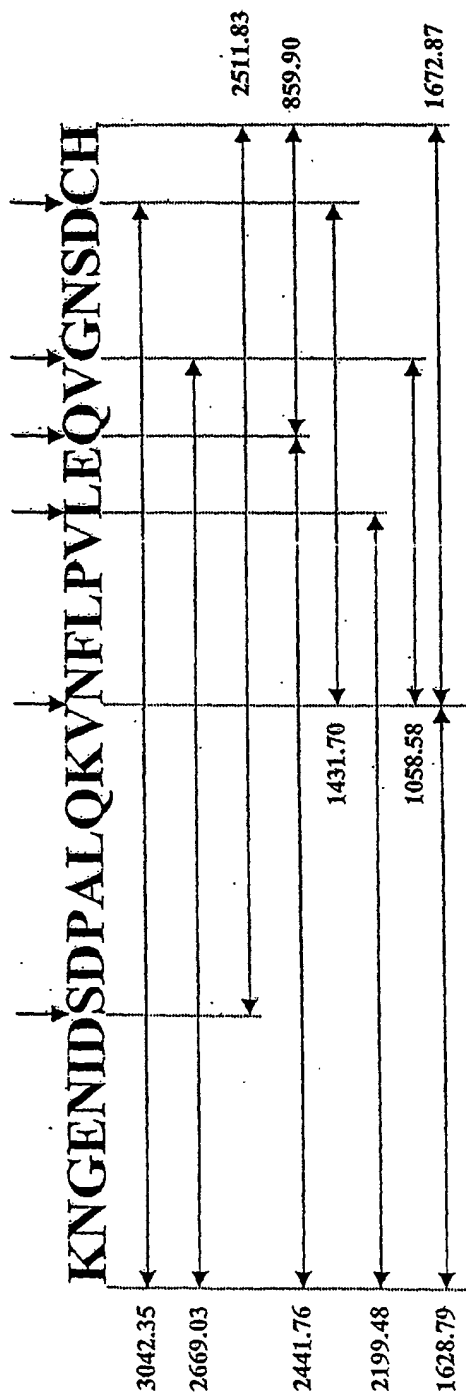


Figure 54

SCP-1 (201-227)

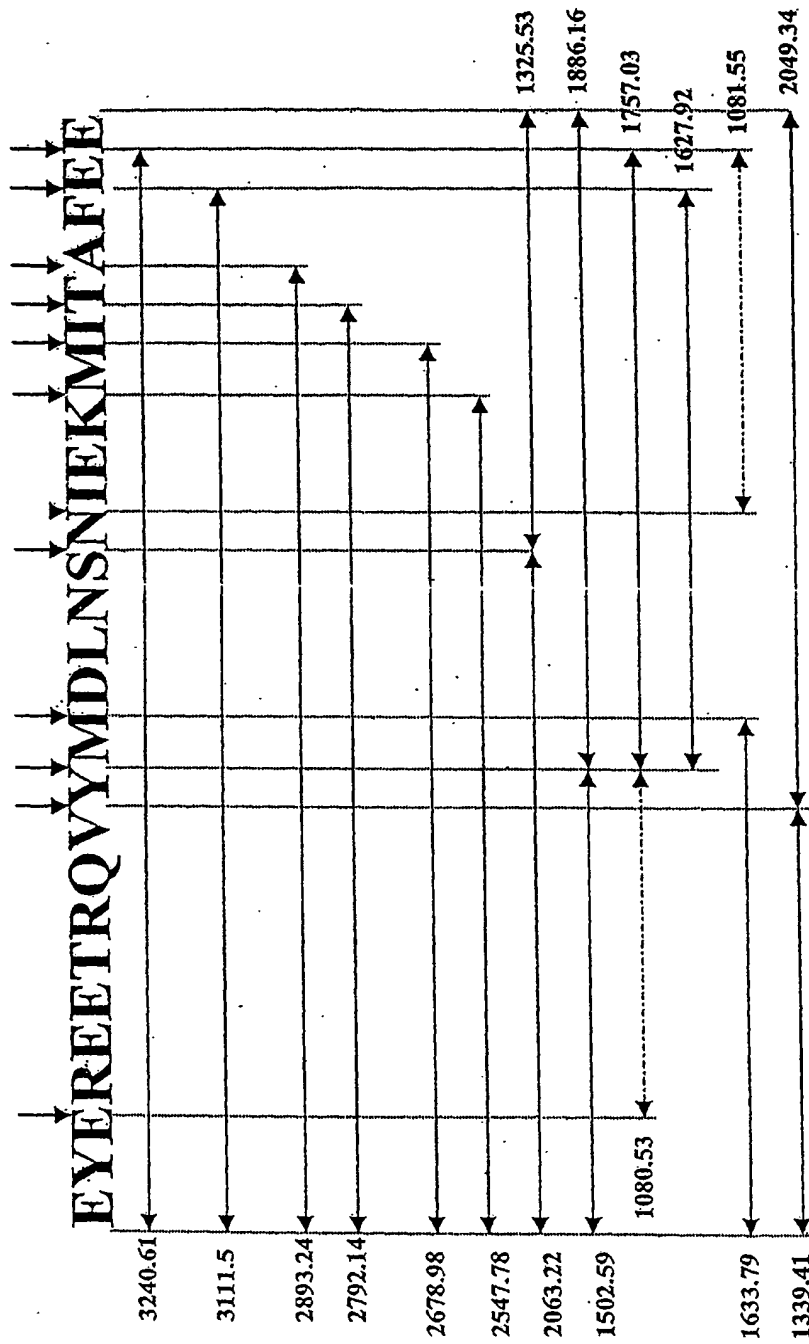


Figure 55

SCP-1 (395-424)

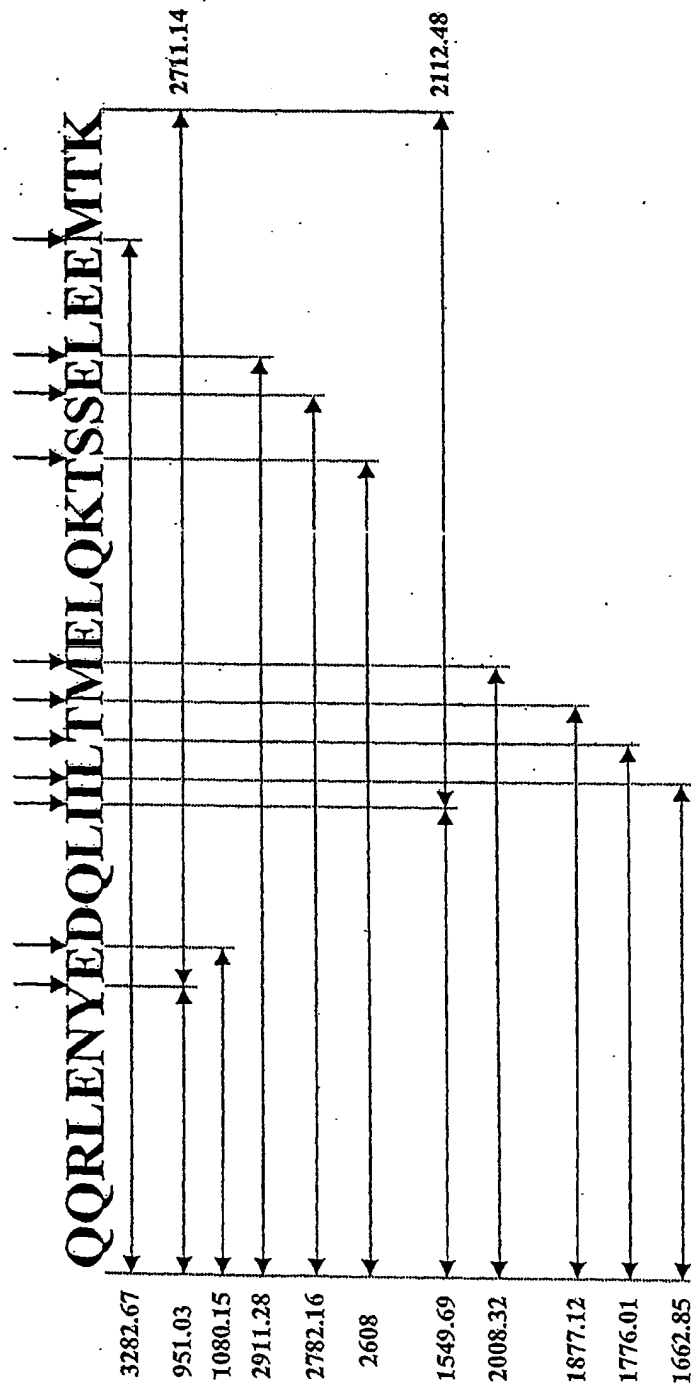


Figure S6

SCP-1 (416-442)

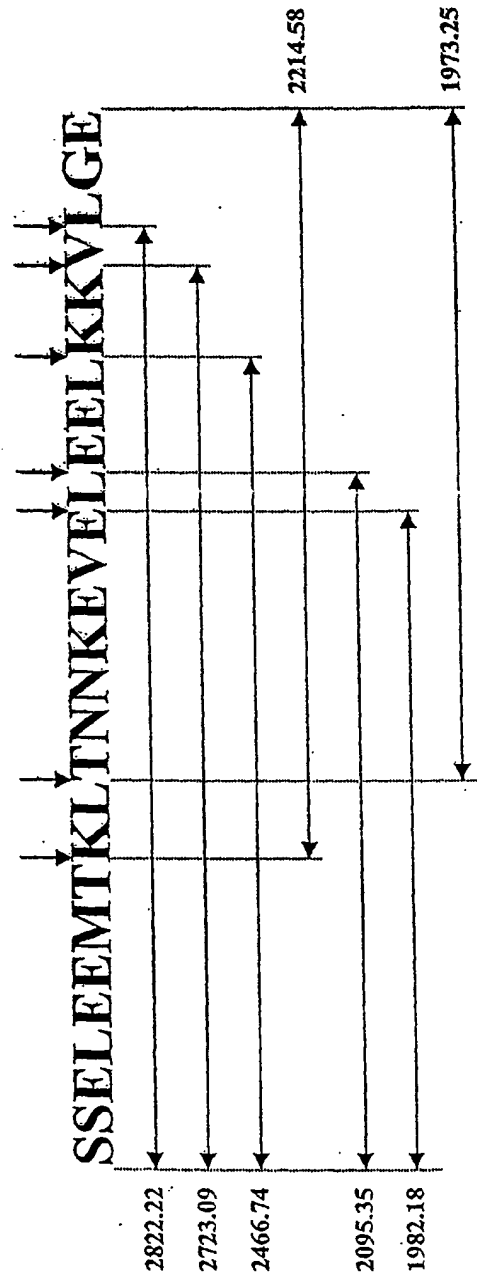


Figure 57

SCP-1 (518-545)

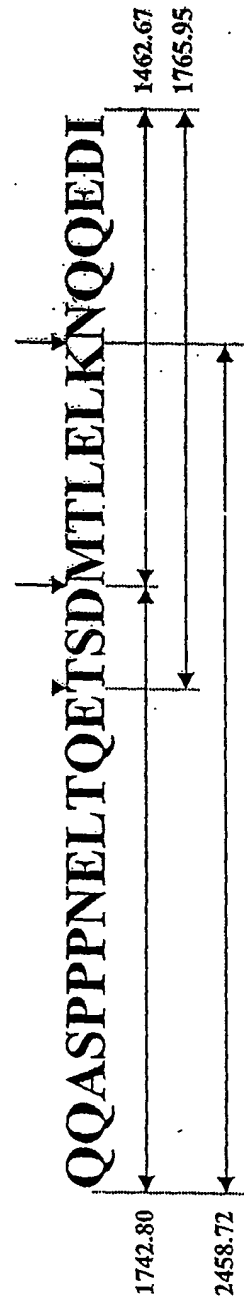


Figure 58

SCP-1 (545-578)

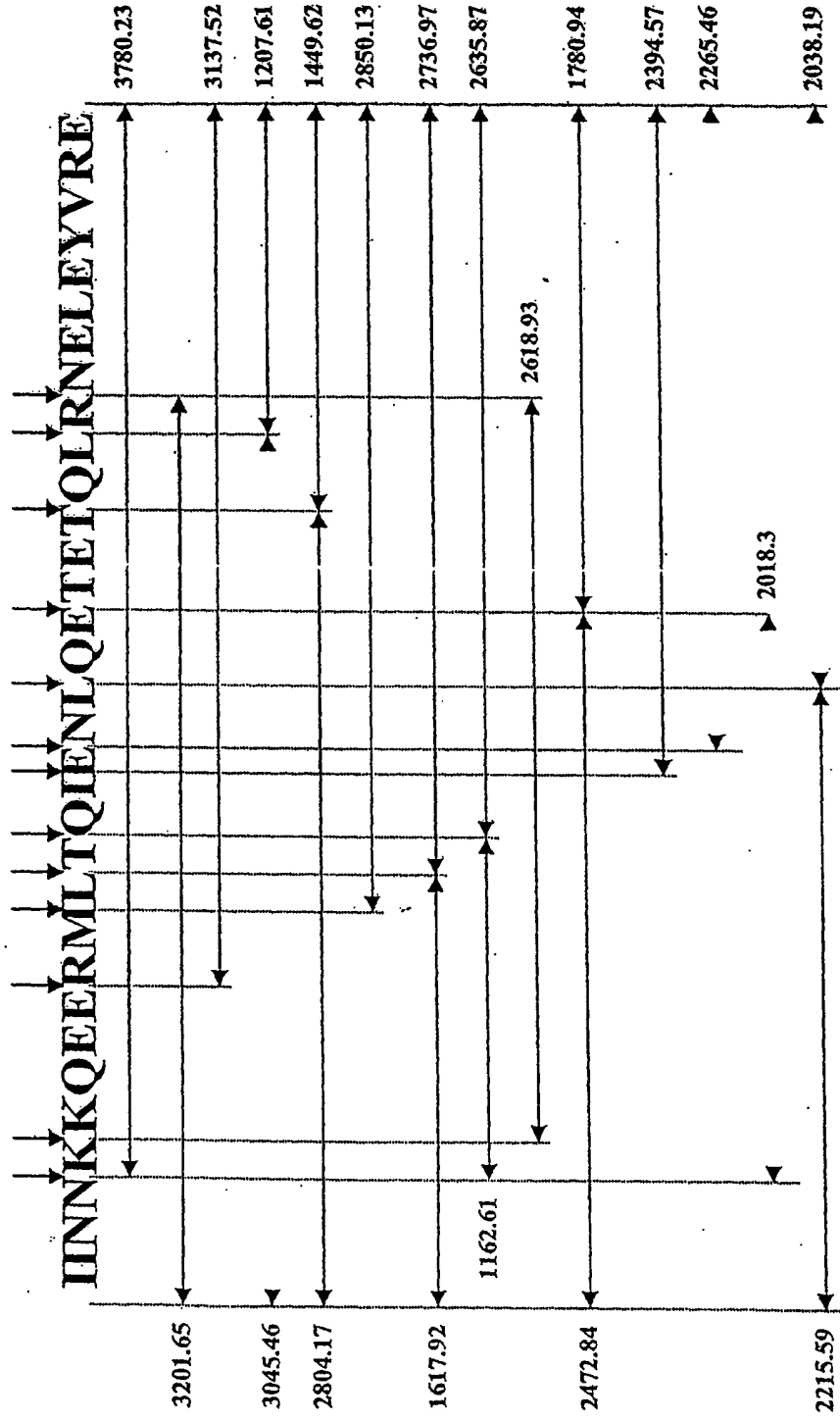


Figure 59

SCP-1 (559-585)

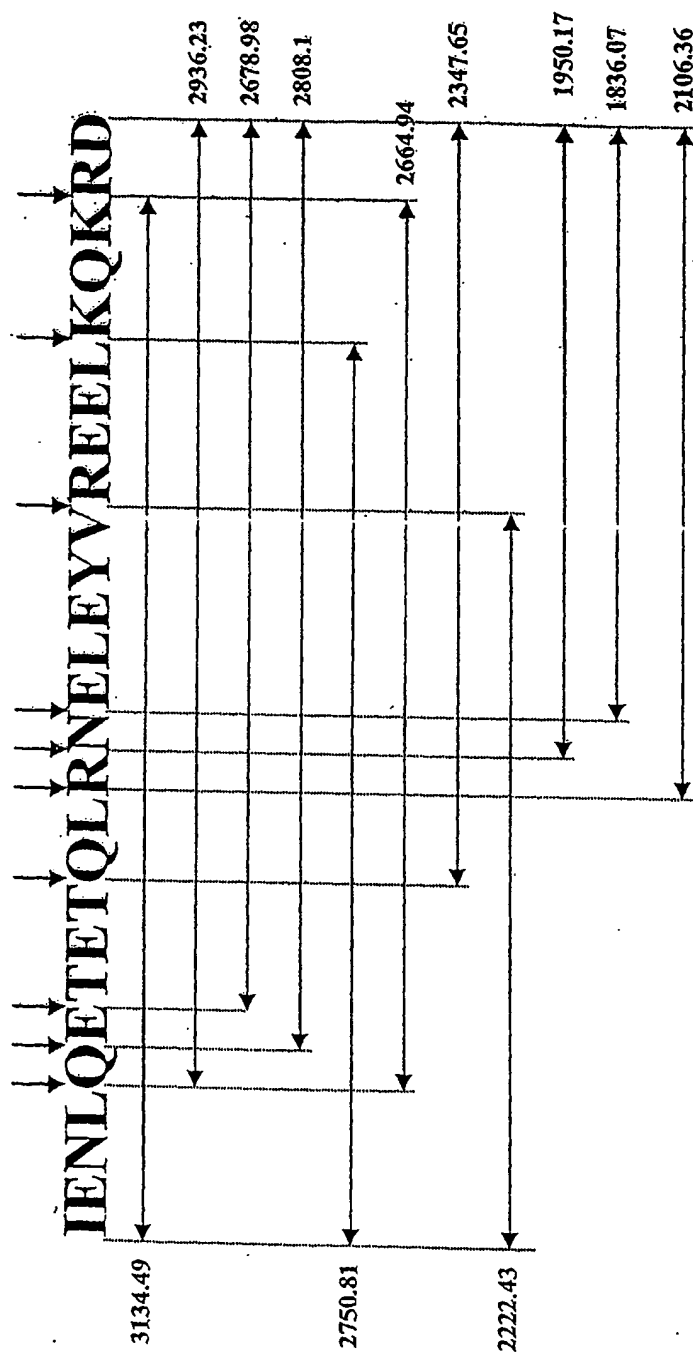


Figure 60

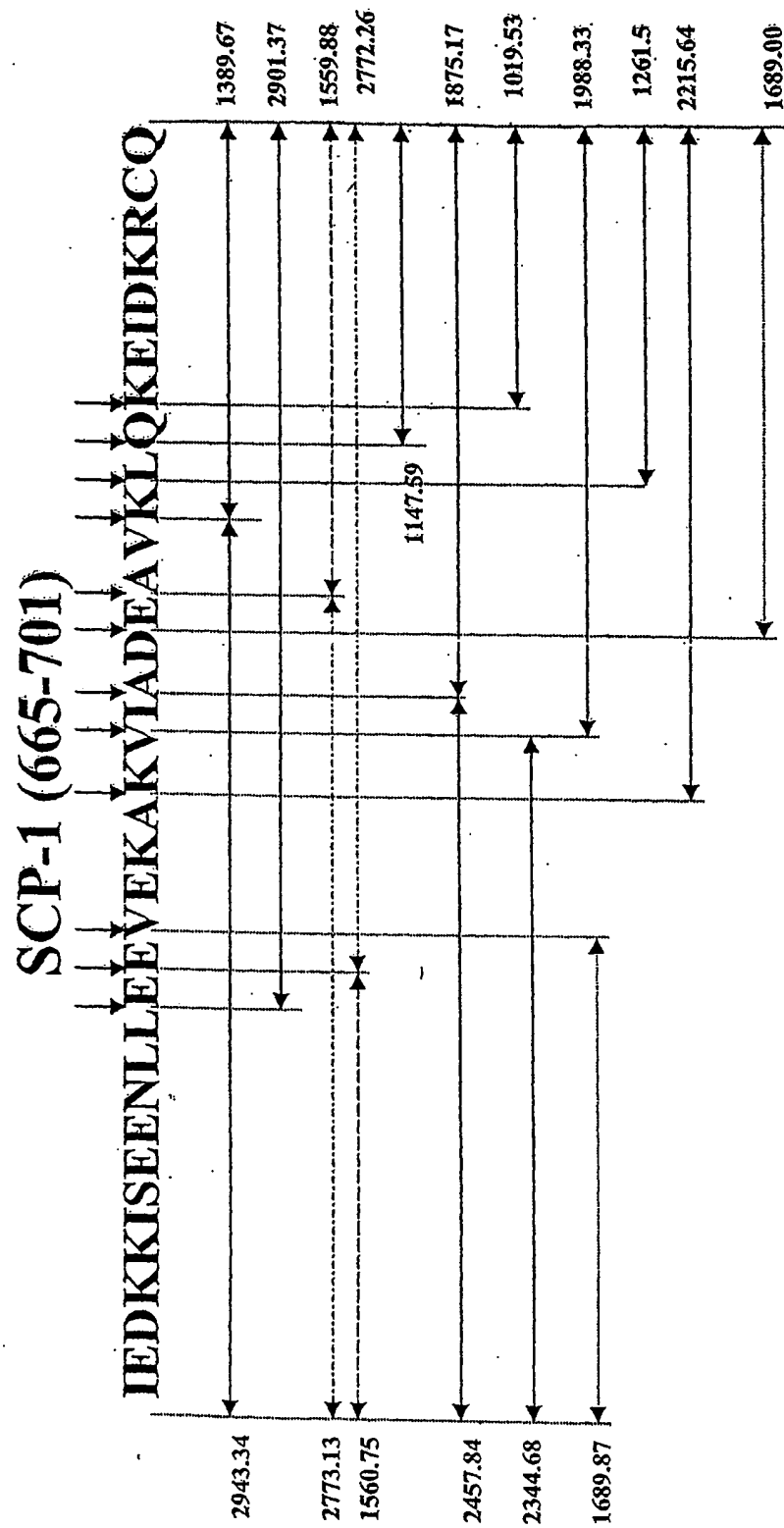


Figure 61

SCP-1 (694-720)

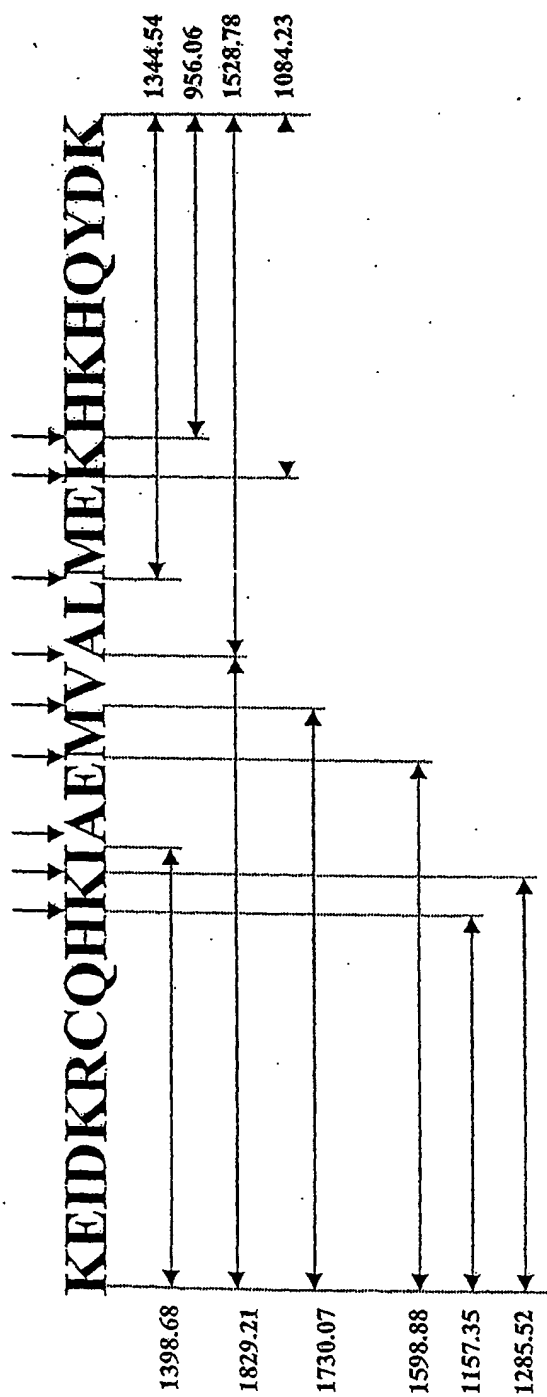


Figure 62

SCP-1 735-769

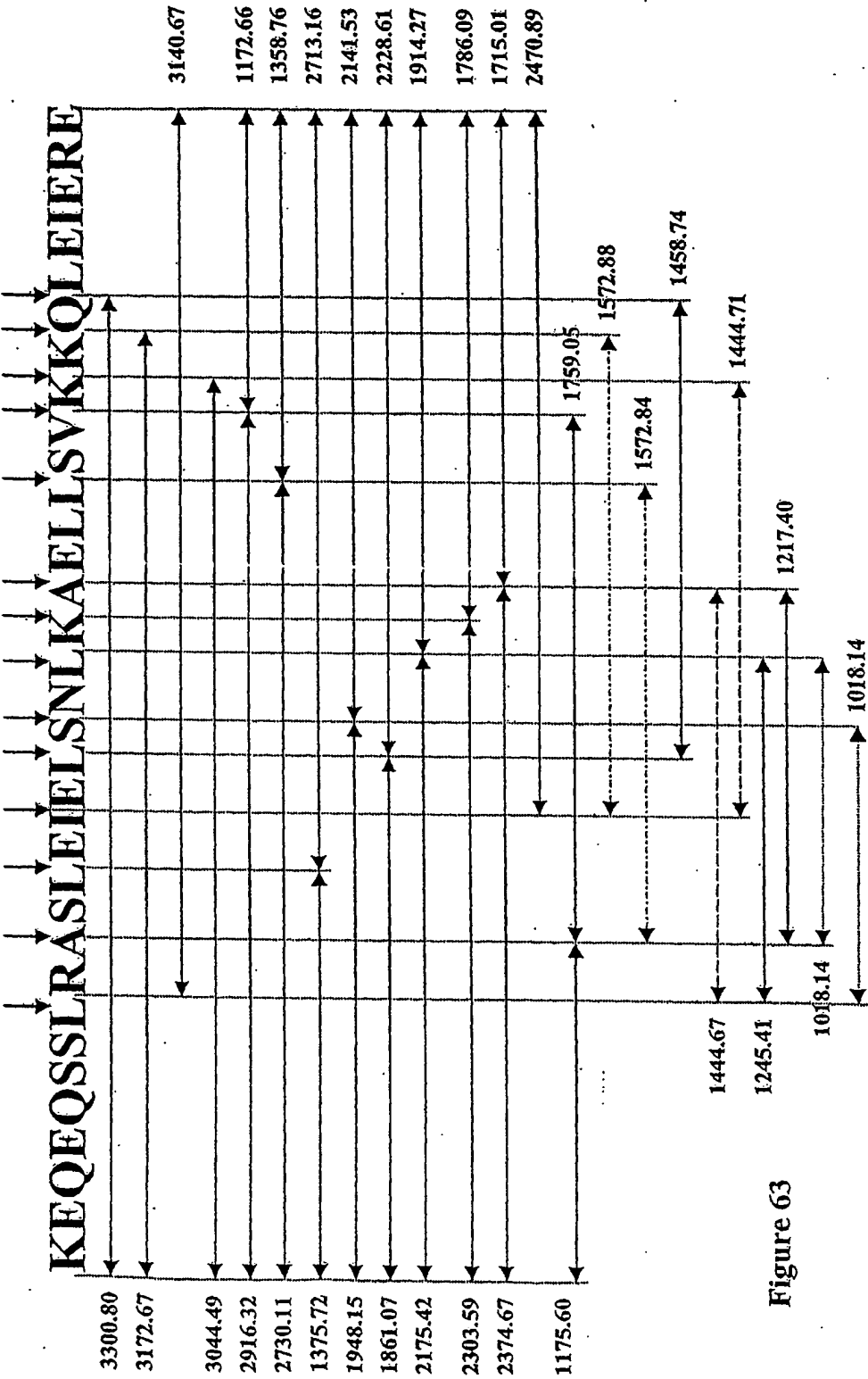


Figure 63

SCP-1 (786-816)

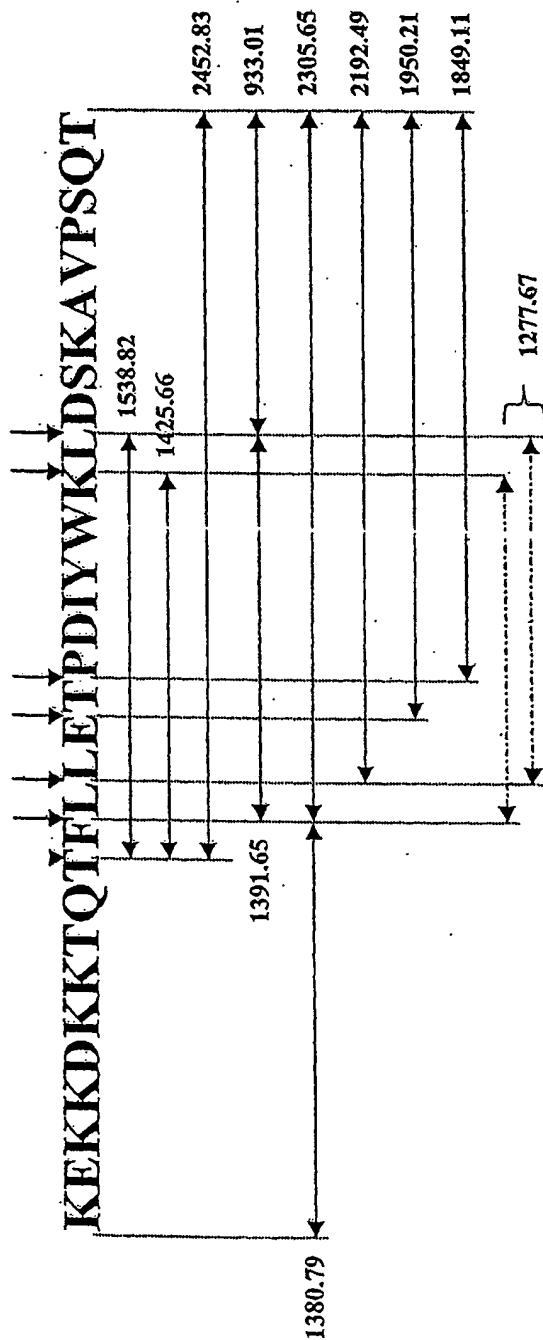


Figure 64

SCP-1 (806-833)

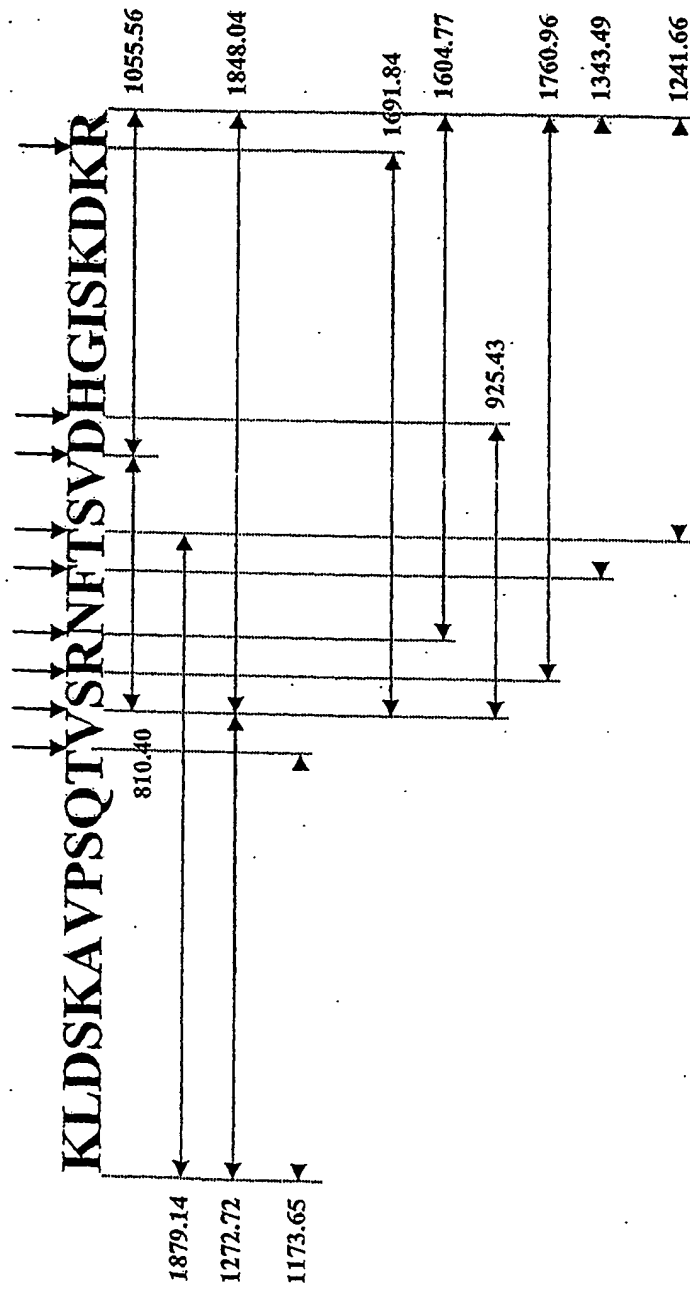


Figure 65

SCP-1 (826-853)

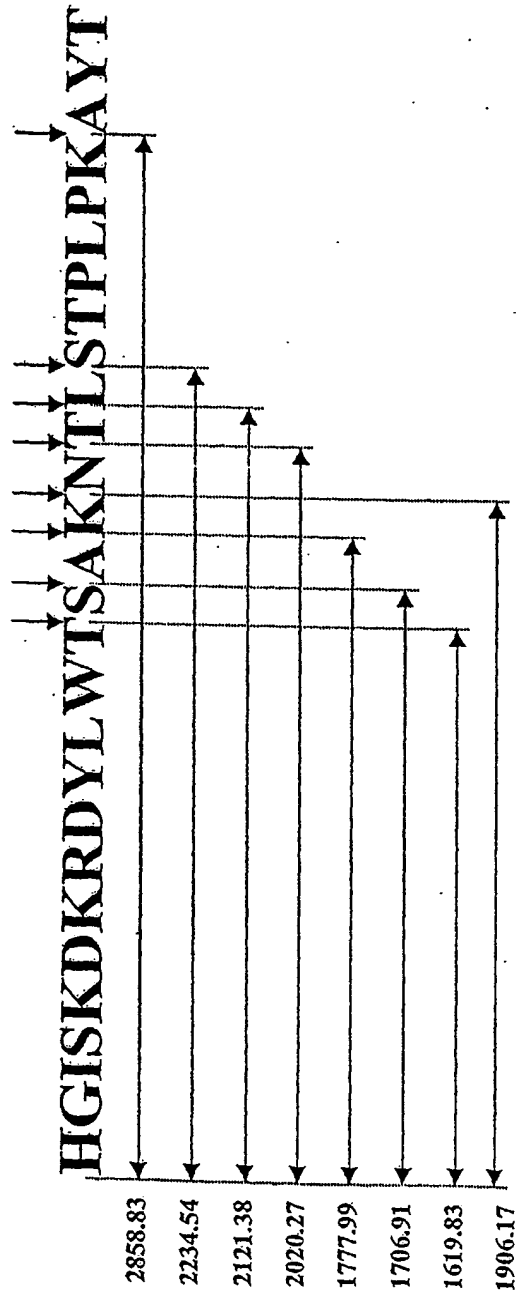


Figure 66

SCP-1 (832-859)

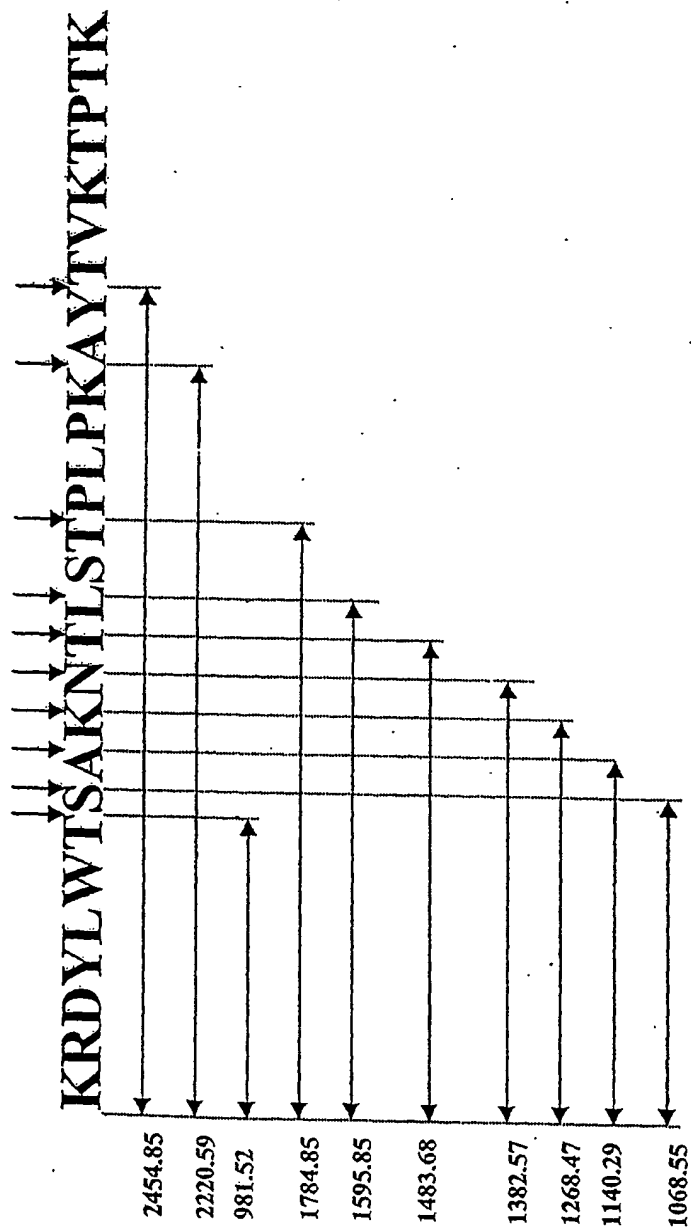


Figure 67

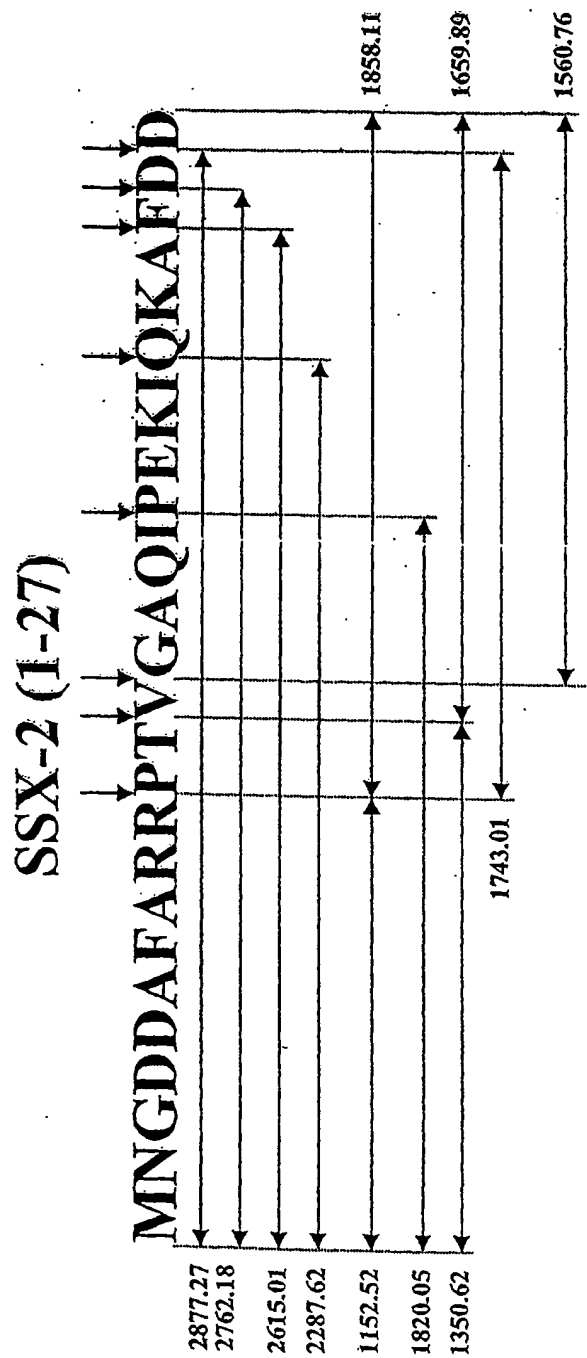


Figure 68

Survivin (116-142)

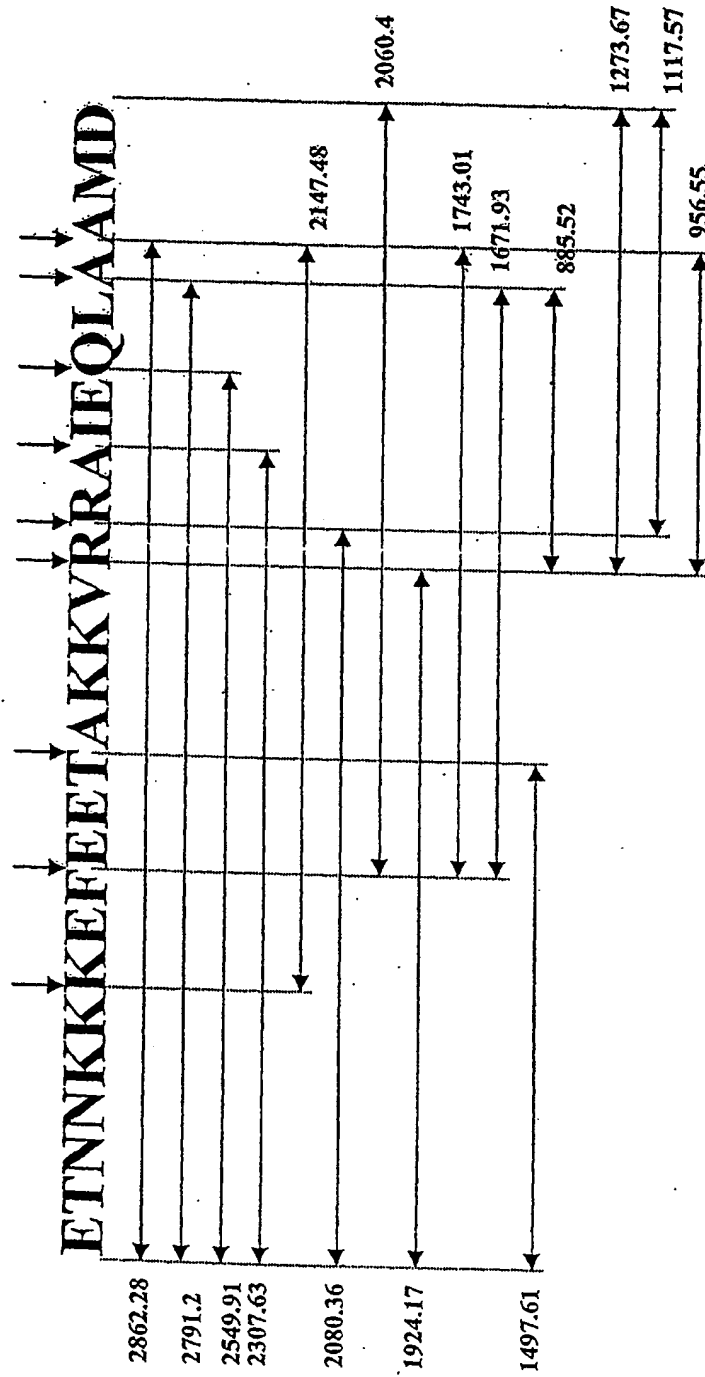


Figure 69

BAGE (1-35)

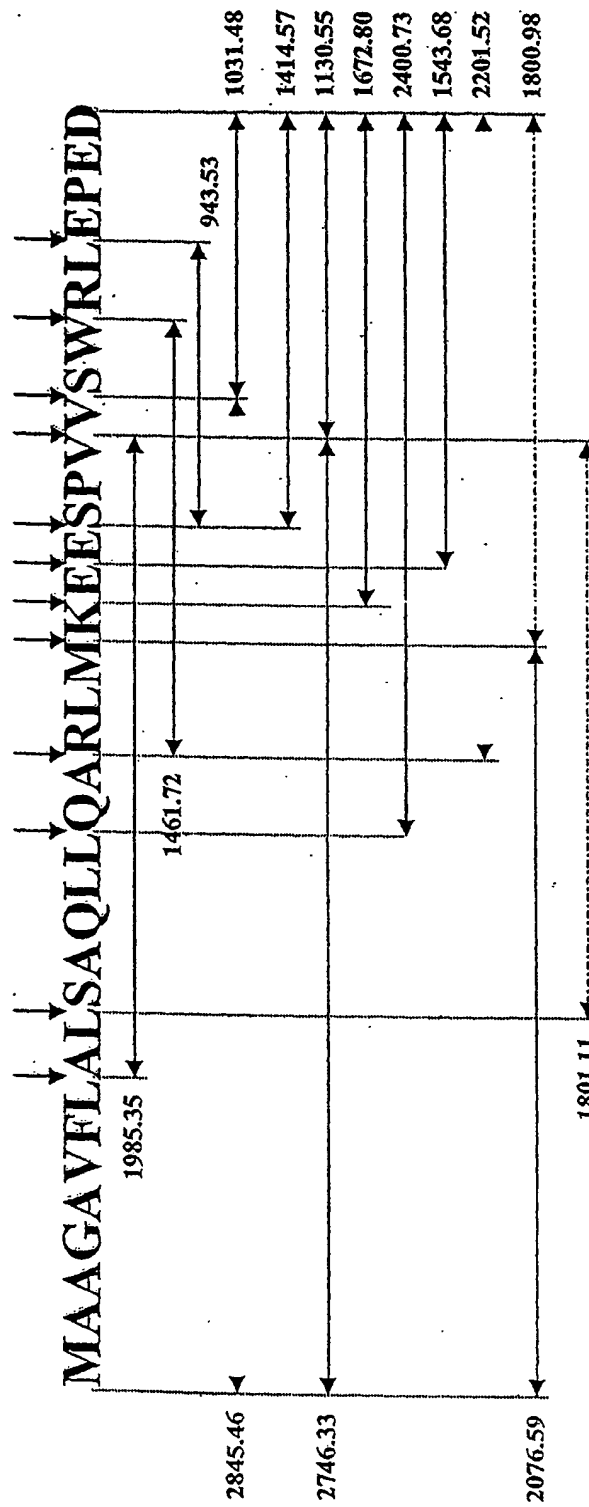


Figure 70

SEQUENCE LISTING

<110> MANNKIND CORPORATION
 SIMARD, John J. L.
 DIAMOND, David C.
 LIU, Liping
 LIU, Zheng

<120> EPITOPE SEQUENCES

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Thr	Glu	Arg	Arg	Leu	Leu	Val	Arg	Arg	Asn	Ile	Phe	Asp	Leu	Ser	Ala
		115					120					125			
Pro	Glu	Lys	Asp	Lys	Phe	Phe	Ala	Tyr	Leu	Thr	Leu	Ala	Lys	His	Thr
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Ile	Ser	Ser	Asp	Tyr	Val	Ile	Pro	Ile	Gly	Thr	Tyr	Gly	Gln	Met	Lys
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Asn	Gly	Ser	Thr	Pro	Met	Phe	Asn	Asp	Ile	Asn	Ile	Tyr	Asp	Leu	Phe
				165				170					175		
Val	Trp	Met	His	Tyr	Tyr	Val	Ser	Met	Asp	Ala	Leu	Leu	Gly	Gly	Ser
			180					185					190		

Glu Ile Trp Arg Asp Ile Asp Phe Ala His Glu Ala Pro Ala Phe Leu
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 Pro Trp His Arg Leu Phe Leu Leu Arg Trp Glu Gln Glu Ile Gln Lys
 210 215 220
 Leu Thr Gly Asp Glu Asn Phe Thr Ile Pro Tyr Trp Asp Trp Arg Asp
 225 230 235 240
 Ala Glu Lys Cys Asp Ile Cys Thr Asp Glu Tyr Met Gly Gly Gln His
 245 250 255
 Pro Thr Asn Pro Asn Leu Leu Ser Pro Ala Ser Phe Phe Ser Ser Trp
 260 265 270
 Gln Ile Val Cys Ser Arg Leu Glu Tyr Asn Ser His Gln Ser Leu
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 Cys Asn Gly Thr Pro Glu Gly Pro Leu Arg Arg Asn Pro Gly Asn His
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 Asp Lys Ser Arg Thr Pro Arg Leu Pro Ser Ser Ala Asp Val Glu Phe
 305 310 315 320
 Cys Leu Ser Leu Thr Gln Tyr Glu Ser Gly Ser Met Asp Lys Ala Ala
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 Gly Ile Ala Asp Ala Ser Gln Ser Ser Met His Asn Ala Leu His Ile
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 Tyr Met Asn Gly Thr Met Ser Gln Val Gln Gly Ser Ala Asn Asp Pro
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 385 390 395 400
 Leu Arg Arg His Arg Pro Leu Gln Glu Val Tyr Pro Glu Ala Asn Ala
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 Pro Ile Gly His Asn Arg Glu Ser Tyr Met Val Pro Phe Ile Pro Leu
 420 425 430
 Tyr Arg Asn Gly Asp Phe Phe Ile Ser Ser Lys Asp Leu Gly Tyr Asp
 435 440 445
 Tyr Ser Tyr Leu Gln Asp Ser Asp Pro Asp Ser Phe Gln Asp Tyr Ile
 450 455 460
 Lys Ser Tyr Leu Glu Gln Ala Ser Arg Ile Trp Ser Trp Leu Leu Gly
 465 470 475 480
 Ala Ala Met Val Gly Ala Val Leu Thr Ala Leu Leu Ala Gly Leu Val
 485 490 495
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<211> 188

<212> PRT

<213> Homo sapiens

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 Ser Lys Glu Glu Trp Glu Lys Met Lys Ala Ser Glu Lys Ile Phe Tyr
 35 40 45
 Val Tyr Met Lys Arg Lys Tyr Glu Ala Met Thr Lys Leu Gly Phe Lys
 50 55 60
 Ala Thr Leu Pro Pro Phe Met Cys Asn Lys Arg Ala Glu Asp Phe Gln

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65          70          75          80
Gly Asn Asp Leu Asp Asn Asp Pro Asn Arg Gly Asn Gln Val Glu Arg
      85          90          95
Pro Gln Met Thr Phe Gly Arg Leu Gln Gly Ile Ser Pro Lys Ile Met
      100          105          110
Pro Lys Lys Pro Ala Glu Glu Gly Asn Asp Ser Glu Glu Val Pro Glu
      115          120          125
Ala Ser Gly Pro Gln Asn Asp Gly Lys Glu Leu Cys Pro Pro Gly Lys
      130          135          140
Pro Thr Thr Ser Glu Lys Ile His Glu Arg Ser Gly Pro Lys Arg Gly
145          150          155          160
Glu His Ala Trp Thr His Arg Leu Arg Glu Arg Lys Gln Leu Val Ile
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Tyr Glu Glu Ile Ser Asp Pro Glu Glu Asp Asp Glu
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<212> PRT

<213> Homo sapiens

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Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Asn Glu
      35          40          45
Ala Thr Asn Ile Thr Pro Lys His Asn Met Lys Ala Phe Leu Asp Glu
      50          55          60
Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Gln Ile
65          70          75          80
Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
      85          90          95
Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Ala His
      100          105          110
Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
      115          120          125
Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
      130          135          140
Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Ile Val Pro Pro
145          150          155          160
Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
      165          170          175
Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met
      180          185          190
Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val
      195          200          205
Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Lys Gly
      210          215          220
Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys
225          230          235          240
Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
      245          250          255
Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr
      260          265          270
Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val Gly
      275          280          285
Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln Lys
290          295          300

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Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp Arg
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 Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
 325 330 335
 Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Asn Glu Val
 340 345 350
 Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu Pro
 355 360 365
 Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly
 370 375 380
 Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val Arg
 385 390 395 400
 Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr Ile
 405 410 415
 Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser Thr
 420 425 430
 Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val Ala
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 Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val
 450 455 460
 Asp Cys Thr Pro Leu Met Tyr Ser Leu Val His Asn Leu Thr Lys Glu
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 Leu Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu Ser
 485 490 495
 Trp Thr Lys Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg Ile
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 515 520 525
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 530 535 540
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 Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Ile Val
 580 585 590
 Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr Ala
 595 600 605
 Asp Lys Ile Tyr Ser Ile Ser Met Lys His Pro Gln Glu Met Lys Thr
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 Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe Thr
 625 630 635 640
 Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Phe Asp Lys Ser
 645 650 655
 Asn Pro Ile Val Leu Arg Met Met Asn Asp Gln Leu Met Phe Leu Glu
 660 665 670
 Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg
 675 680 685
 His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
 690 695 700
 Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp
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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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Phe Lys Ala Thr Leu Pro
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Met Lys Ala Ser Glu Lys Ile Phe Tyr
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Lys Tyr Ser Glu Lys Ile Ser Tyr Val
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<210> 27
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Lys Val Ser Glu Lys Ile Val Tyr Val
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<210> 28

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<400> 28

Lys Ser Ser Glu Lys Ile Val Tyr Val
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<210> 29

<211> 9

<212> PRT

<213> Homo sapiens

<400> 29

Lys Ala Ser Glu Lys Ile Ile Tyr Val
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<210> 30

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<212> PRT

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<210> 33
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<400> 33
Gly Met Pro Glu Gly Asp Leu Val Tyr Val
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<210> 34
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<210> 35
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Met Pro Glu Gly Asp Leu Val Tyr
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<210> 45

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Tyr Tyr Asp Ala Gln Lys Leu Leu Glu
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1 5

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1 5 10

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<400> 49
Ile Gly Tyr Tyr Asp Ala Gln Lys Leu
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<400> 50
Pro Ile Gly Tyr Tyr Asp Ala Gln Lys Leu
1 5 10

<210> 51
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 51
 Ser Ile Pro Val His Pro Ile Gly Tyr
 1 5

<210> 52
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 52
 Pro Ser Ile Pro Val His Pro Ile Gly Tyr
 1 5 10

<210> 53
 <211> 8
 <212> PRT
 <213> Homo sapiens

<400> 53
 Ile Pro Val His Pro Ile Gly Tyr
 1 5

<210> 54
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 54
 Tyr Tyr Asp Ala Gln Lys Leu Leu Glu
 1 5

<210> 55
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 55
 Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val Asp Cys Thr Pro Leu
 1 5 10 15
 Met Tyr Ser Leu Val His Leu Thr Lys Glu Leu
 20 25

<210> 56
 <211> 9
 <212> PRT
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<400> 56
 Ile Glu Gly Asn Tyr Thr Leu Arg Val

1 5

<210> 57
<211> 10
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<213> Homo sapiens

<400> 57
Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val
1 5 10

<210> 58
<211> 8
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<400> 58
Glu Gly Asn Tyr Thr Leu Arg Val
1 5

<210> 59
<211> 9
<212> PRT
<213> Homo sapiens

<400> 59
Thr Leu Arg Val Asp Cys Thr Pro Leu
1 5

<210> 60
<211> 10
<212> PRT
<213> Homo sapiens

<400> 60
Tyr Thr Leu Arg Val Asp Cys Thr Pro Leu
1 5 10

<210> 61
<211> 9
<212> PRT
<213> Homo sapiens

<400> 61
Leu Arg Val Asp Cys Thr Pro Leu Met
1 5

<210> 62
<211> 9
<212> PRT
<213> Homo sapiens

<400> 62
Arg Val Asp Cys Thr Pro Leu Met Tyr
1 5

<210> 63
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 63
 Leu Arg Val Asp Cys Thr Pro Leu Met Tyr
 1 5 10

<210> 64
 <211> 35
 <212> PRT
 <213> Homo sapiens

<400> 64
 Phe Asp Lys Ser Asn Pro Ile Val Leu Arg Met Met Asn Asp Gln Leu
 1 5 10 15
 Met Phe Leu Glu Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg
 20 25 30
 Pro Phe Tyr
 35

<210> 65
 <211> 22
 <212> PRT
 <213> Homo sapiens

<400> 65
 Val Leu Arg Met Met Asn Asp Gln Leu Met Phe Leu Glu Arg Ala Phe
 1 5 10 15
 Ile Asp Pro Leu Gly Leu
 20

<210> 66
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 66
 Met Met Asn Asp Gln Leu Met Phe Leu
 1 5

<210> 67
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 67
 Arg Met Met Asn Asp Gln Leu Met Phe Leu
 1 5 10

<210> 68
 <211> 9
 <212> PRT

<213> Homo sapiens

<400> 68

Arg Met Met Asn Asp Gln Leu Met Phe
1 5

<210> 69

<211> 17

<212> PRT

<213> Homo sapiens

<400> 69

Met Leu Leu Ala Val Leu Tyr Cys Leu Leu Trp Ser Phe Gln Thr Ser
1 5 10 15
Ala

<210> 70

<211> 661

<212> PRT

<213> Homo sapiens

<400> 70

Met Asp Leu Val Leu Lys Arg Cys Leu Leu His Leu Ala Val Ile Gly
1 5 10 15
Ala Leu Leu Ala Val Gly Ala Thr Lys Val Pro Arg Asn Gln Asp Trp
20 25 30
Leu Gly Val Ser Arg Gln Leu Arg Thr Lys Ala Trp Asn Arg Gln Leu
35 40 45
Tyr Pro Glu Trp Thr Glu Ala Gln Arg Leu Asp Cys Trp Arg Gly Gly
50 55 60
Gln Val Ser Leu Lys Val Ser Asn Asp Gly Pro Thr Leu Ile Gly Ala
65 70 75 80
Asn Ala Ser Phe Ser Ile Ala Leu Asn Phe Pro Gly Ser Gln Lys Val
85 90 95
Leu Pro Asp Gly Gln Val Ile Trp Val Asn Asn Thr Ile Ile Asn Gly
100 105 110
Ser Gln Val Trp Gly Gly Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp
115 120 125
Ala Cys Ile Phe Pro Asp Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser
130 135 140
Gln Lys Arg Ser Phe Val Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp
145 150 155 160
Gln Val Leu Gly Gly Pro Val Ser Gly Leu Ser Ile Gly Thr Gly Arg
165 170 175
Ala Met Leu Gly Thr His Thr Met Glu Val Thr Val Tyr His Arg Arg
180 185 190
Gly Ser Arg Ser Tyr Val Pro Leu Ala His Ser Ser Ser Ala Phe Thr
195 200 205
Ile Thr Asp Gln Val Pro Phe Ser Val Ser Val Ser Gln Leu Arg Ala
210 215 220
Leu Asp Gly Gly Asn Lys His Phe Leu Arg Asn Gln Pro Leu Thr Phe
225 230 235 240
Ala Leu Gln Leu His Asp Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu
245 250 255
Ser Tyr Thr Trp Asp Phe Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg
260 265 270
Ala Pro Val Val Thr His Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala
275 280 285

Gln Val Val Leu Gln Ala Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser
 290 295 300
 Pro Val Pro Gly Thr Thr Asp Gly His Arg Pro Thr Ala Glu Ala Pro
 305 310 315 320
 Asn Thr Thr Ala Gly Gln Val Pro Thr Thr Glu Val Val Gly Thr Thr
 325 330 335
 Pro Gly Gln Ala Pro Thr Ala Glu Pro Ser Gly Thr Thr Ser Val Gln
 340 345 350
 Val Pro Thr Thr Glu Val Ile Ser Thr Ala Pro Val Gln Met Pro Thr
 355 360 365
 Ala Glu Ser Thr Gly Met Thr Pro Glu Lys Val Pro Val Ser Glu Val
 370 375 380
 Met Gly Thr Thr Leu Ala Glu Met Ser Thr Pro Glu Ala Thr Gly Met
 385 390 395 400
 Thr Pro Ala Glu Val Ser Ile Val Val Leu Ser Gly Thr Thr Ala Ala
 405 410 415
 Gln Val Thr Thr Thr Glu Trp Val Glu Thr Thr Ala Arg Glu Leu Pro
 420 425 430
 Ile Pro Glu Pro Glu Gly Pro Asp Ala Ser Ser Ile Met Ser Thr Glu
 435 440 445
 Ser Ile Thr Gly Ser Leu Gly Pro Leu Leu Asp Gly Thr Ala Thr Leu
 450 455 460
 Arg Leu Val Lys Arg Gln Val Pro Leu Asp Cys Val Leu Tyr Arg Tyr
 465 470 475 480
 Gly Ser Phe Ser Val Thr Leu Asp Ile Val Gln Gly Ile Glu Ser Ala
 485 490 495
 Glu Ile Leu Gln Ala Val Pro Ser Gly Glu Gly Asp Ala Phe Glu Leu
 500 505 510
 Thr Val Ser Cys Gln Gly Gly Leu Pro Lys Glu Ala Cys Met Glu Ile
 515 520 525
 Ser Ser Pro Gly Cys Gln Pro Pro Ala Gln Arg Leu Cys Gln Pro Val
 530 535 540
 Leu Pro Ser Pro Ala Cys Gln Leu Val Leu His Gln Ile Leu Lys Gly
 545 550 555 560
 Gly Ser Gly Thr Tyr Cys Leu Asn Val Ser Leu Ala Asp Thr Asn Ser
 565 570 575
 Leu Ala Val Val Ser Thr Gln Leu Ile Met Pro Gly Gln Glu Ala Gly
 580 585 590
 Leu Gly Gln Val Pro Leu Ile Val Gly Ile Leu Leu Val Leu Met Ala
 595 600 605
 Val Val Leu Ala Ser Leu Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp
 610 615 620
 Phe Ser Val Pro Gln Leu Pro His Ser Ser Ser His Trp Leu Arg Leu
 625 630 635 640
 Pro Arg Ile Phe Cys Ser Cys Pro Ile Gly Glu Asn Ser Pro Leu Leu
 645 650 655
 Ser Gly Gln Gln Val
 660

<210> 71

<211> 309

<212> PRT

<213> Homo sapiens

<400> 71

Met Ser Leu Glu Gln Arg Ser Leu His Cys Lys Pro Glu Glu Ala Leu
 1 5 10 15
 Glu Ala Gln Gln Glu Ala Leu Gly Leu Val Cys Val Gln Ala Ala Thr
 20 25 30
 Ser Ser Ser Ser Pro Leu Val Leu Gly Thr Leu Glu Glu Val Pro Thr

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      35      40      45
Ala Gly Ser Thr Asp Pro Pro Gln Ser Pro Gln Gly Ala Ser Ala Phe
  50      55      60
Pro Thr Thr Ile Asn Phe Thr Arg Gln Arg Gln Pro Ser Glu Gly Ser
  65      70      75      80
Ser Ser Arg Glu Glu Glu Gly Pro Ser Thr Ser Cys Ile Leu Glu Ser
      85      90      95
Leu Phe Arg Ala Val Ile Thr Lys Lys Val Ala Asp Leu Val Gly Phe
      100      105      110
Leu Leu Leu Lys Tyr Arg Ala Arg Glu Pro Val Thr Lys Ala Glu Met
      115      120      125
Leu Glu Ser Val Ile Lys Asn Tyr Lys His Cys Phe Pro Glu Ile Phe
      130      135      140
Gly Lys Ala Ser Glu Ser Leu Gln Leu Val Phe Gly Ile Asp Val Lys
      145      150      155      160
Glu Ala Asp Pro Thr Gly His Ser Tyr Val Leu Val Thr Cys Leu Gly
      165      170      175
Leu Ser Tyr Asp Gly Leu Leu Gly Asp Asn Gln Ile Met Pro Lys Thr
      180      185      190
Gly Phe Leu Ile Ile Val Leu Val Met Ile Ala Met Glu Gly Gly His
      195      200      205
Ala Pro Glu Glu Glu Ile Trp Glu Glu Leu Ser Val Met Glu Val Tyr
      210      215      220
Asp Gly Arg Glu His Ser Ala Tyr Gly Glu Pro Arg Lys Leu Leu Thr
      225      230      235      240
Gln Asp Leu Val Gln Glu Lys Tyr Leu Glu Tyr Arg Gln Val Pro Asp
      245      250      255
Ser Asp Pro Ala Arg Tyr Glu Phe Leu Trp Gly Pro Arg Ala Leu Ala
      260      265      270
Glu Thr Ser Tyr Val Lys Val Leu Glu Tyr Val Ile Lys Val Ser Ala
      275      280      285
Arg Val Arg Phe Phe Phe Pro Ser Leu Arg Glu Ala Ala Leu Arg Glu
      290      295      300
Glu Glu Glu Gly Val
      305

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<210> 72

<211> 314

<212> PRT

<213> Homo sapiens

<400> 72

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Met Pro Leu Glu Gln Arg Ser Gln His Cys Lys Pro Glu Glu Gly Leu
  1      5      10      15
Glu Ala Arg Gly Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Ala
      20      25      30
Thr Glu Glu Gln Gln Thr Ala Ser Ser Ser Thr Leu Val Glu Val
      35      40      45
Thr Leu Gly Glu Val Pro Ala Ala Asp Ser Pro Ser Pro Pro His Ser
      50      55      60
Pro Gln Gly Ala Ser Ser Phe Ser Thr Thr Ile Asn Tyr Thr Leu Trp
      65      70      75      80
Arg Gln Ser Asp Glu Gly Ser Ser Asn Gln Glu Glu Gly Pro Arg
      85      90      95
Met Phe Pro Asp Leu Glu Ser Glu Phe Gln Ala Ala Ile Ser Arg Lys
      100      105      110
Met Val Glu Leu Val His Phe Leu Leu Lys Tyr Arg Ala Arg Glu
      115      120      125
Pro Val Thr Lys Ala Glu Met Leu Glu Ser Val Leu Arg Asn Cys Gln
      130      135      140

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Asp Phe Phe Pro Val Ile Phe Ser Lys Ala Ser Glu Tyr Leu Gln Leu
 145 150 155 160
 Val Phe Gly Ile Glu Val Val Glu Val Val Pro Ile Ser His Leu Tyr
 165 170 175
 Ile Leu Val Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly Asp
 180 185 190
 Asn Gln Val Met Pro Lys Thr Gly Leu Leu Ile Ile Val Leu Ala Ile
 195 200 205
 Ile Ala Ile Glu Gly Asp Cys Ala Pro Glu Glu Lys Ile Trp Glu Glu
 210 215 220
 Leu Ser Met Leu Glu Val Phe Glu Gly Arg Glu Asp Ser Val Phe Ala
 225 230 235 240
 His Pro Arg Lys Leu Leu Met Gln Asp Leu Val Gln Glu Asn Tyr Leu
 245 250 255
 Glu Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala Cys Tyr Glu Phe Leu
 260 265 270
 Trp Gly Pro Arg Ala Leu Ile Glu Thr Ser Tyr Val Lys Val Leu His
 275 280 285
 His Thr Leu Lys Ile Gly Gly Glu Pro His Ile Ser Tyr Pro Pro Leu
 290 295 300
 His Glu Arg Ala Leu Arg Glu Gly Glu Glu
 305 310

<210> 73

<211> 314

<212> PRT

<213> Homo sapiens

<400> 73

Met Pro Leu Glu Gln Arg Ser Gln His Cys Lys Pro Glu Glu Gly Leu
 1 5 10 15
 Glu Ala Arg Gly Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Ala
 20 25 30
 Thr Glu Glu Gln Glu Ala Ala Ser Ser Ser Ser Thr Leu Val Glu Val
 35 40 45
 Thr Leu Gly Glu Val Pro Ala Glu Ser Pro Asp Pro Pro Gln Ser
 50 55 60
 Pro Gln Gly Ala Ser Ser Leu Pro Thr Thr Met Asn Tyr Pro Leu Trp
 65 70 75 80
 Ser Gln Ser Tyr Glu Asp Ser Ser Asn Gln Glu Glu Glu Gly Pro Ser
 85 90 95
 Thr Phe Pro Asp Leu Glu Ser Glu Phe Gln Ala Ala Leu Ser Arg Lys
 100 105 110
 Val Ala Glu Leu Val His Phe Leu Leu Leu Lys Tyr Arg Ala Arg Glu
 115 120 125
 Pro Val Thr Lys Ala Glu Met Leu Gly Ser Val Val Gly Asn Trp Gln
 130 135 140
 Tyr Phe Phe Pro Val Ile Phe Ser Lys Ala Ser Ser Ser Leu Gln Leu
 145 150 155 160
 Val Phe Gly Ile Glu Leu Met Glu Val Asp Pro Ile Gly His Leu Tyr
 165 170 175
 Ile Phe Ala Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly Asp
 180 185 190
 Asn Gln Ile Met Pro Lys Ala Gly Leu Leu Ile Ile Val Leu Ala Ile
 195 200 205
 Ile Ala Arg Glu Gly Asp Cys Ala Pro Glu Glu Lys Ile Trp Glu Glu
 210 215 220
 Leu Ser Val Leu Glu Val Phe Glu Gly Arg Glu Asp Ser Ile Leu Gly
 225 230 235 240
 Asp Pro Lys Lys Leu Leu Thr Gln His Phe Val Gln Glu Asn Tyr Leu

245 250 255
 Glu Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala Cys Tyr Glu Phe Leu
 260 265 270
 Trp Gly Pro Arg Ala Leu Val Glu Thr Ser Tyr Val Lys Val Leu His
 275 280 285
 His Met Val Lys Ile Ser Gly Gly Pro His Ile Ser Tyr Pro Pro Leu
 290 295 300
 His Glu Trp Val Leu Arg Glu Gly Glu Glu
 305 310

<210> 74
 <211> 180
 <212> PRT
 <213> Homo sapiens

<400> 74
 Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1 5 10 15
 Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
 20 25 30
 Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
 35 40 45
 Gly Ala Ala Arg Ala Ser Gly Pro Gly Gly Gly Ala Pro Arg Gly Pro
 50 55 60
 His Gly Gly Ala Ala Ser Gly Leu Asn Gly Cys Cys Arg Cys Gly Ala
 65 70 75 80
 Arg Gly Pro Glu Ser Arg Leu Leu Glu Phe Tyr Leu Ala Met Pro Phe
 85 90 95
 Ala Thr Pro Met Glu Ala Glu Leu Ala Arg Arg Ser Leu Ala Gln Asp
 100 105 110
 Ala Pro Pro Leu Pro Val Pro Gly Val Leu Leu Lys Glu Phe Thr Val
 115 120 125
 Ser Gly Asn Ile Leu Thr Ile Arg Leu Thr Ala Ala Asp His Arg Gln
 130 135 140
 Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met
 145 150 155 160
 Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Pro Pro Ser
 165 170 175
 Gly Gln Arg Arg
 180

<210> 75
 <211> 180
 <212> PRT
 <213> Homo sapiens

<400> 75
 Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1 5 10 15
 Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
 20 25 30
 Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
 35 40 45
 Gly Ala Ala Arg Ala Ser Gly Pro Arg Gly Gly Ala Pro Arg Gly Pro
 50 55 60
 His Gly Gly Ala Ala Ser Ala Gln Asp Gly Arg Cys Pro Cys Gly Ala
 65 70 75 80
 Arg Arg Pro Asp Ser Arg Leu Leu Glu Leu His Ile Thr Met Pro Phe
 85 90 95

Ser Ser Pro Met Glu Ala Glu Leu Val Arg Arg Ile Leu Ser Arg Asp
 100 105 110
 Ala Ala Pro Leu Pro Arg Pro Gly Ala Val Leu Lys Asp Phe Thr Val
 115 120 125
 Ser Gly Asn Leu Leu Phe Ile Arg Leu Thr Ala Ala Asp His Arg Gln
 130 135 140
 Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met
 145 150 155 160
 Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Ala Pro Ser
 165 170 175
 Gly Gln Arg Arg
 180

<210> 76
 <211> 210
 <212> PRT
 <213> Homo sapiens

<400> 76
 Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1 5 10 15
 Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
 20 25 30
 Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
 35 40 45
 Gly Ala Ala Arg Ala Ser Gly Pro Arg Gly Gly Ala Pro Arg Gly Pro
 50 55 60
 His Gly Gly Ala Ala Ser Ala Gln Asp Gly Arg Cys Pro Cys Gly Ala
 65 70 75 80
 Arg Arg Pro Asp Ser Arg Leu Leu Glu Leu His Ile Thr Met Pro Phe
 85 90 95
 Ser Ser Pro Met Glu Ala Glu Leu Val Arg Arg Ile Leu Ser Arg Asp
 100 105 110
 Ala Ala Pro Leu Pro Arg Pro Gly Ala Val Leu Lys Asp Phe Thr Val
 115 120 125
 Ser Gly Asn Leu Leu Phe Met Ser Val Trp Asp Gln Asp Arg Glu Gly
 130 135 140
 Ala Gly Arg Met Arg Val Val Gly Trp Gly Leu Gly Ser Ala Ser Pro
 145 150 155 160
 Glu Gly Gln Lys Ala Arg Asp Leu Arg Thr Pro Lys His Lys Val Ser
 165 170 175
 Glu Gln Arg Pro Gly Thr Pro Gly Pro Pro Pro Glu Gly Ala Gln
 180 185 190
 Gly Asp Gly Cys Arg Gly Val Ala Phe Asn Val Met Phe Ser Ala Pro
 195 200 205
 His Ile
 210

<210> 77
 <211> 509
 <212> PRT
 <213> Homo sapiens

<400> 77
 Met Glu Arg Arg Arg Leu Trp Gly Ser Ile Gln Ser Arg Tyr Ile Ser
 1 5 10 15
 Met Ser Val Trp Thr Ser Pro Arg Arg Leu Val Glu Leu Ala Gly Gln
 20 25 30
 Ser Leu Leu Lys Asp Glu Ala Leu Ala Ile Ala Ala Leu Glu Leu Leu

35					40					45					
Pro	Arg	Glu	Leu	Phe	Pro	Pro	Leu	Phe	Met	Ala	Ala	Phe	Asp	Gly	Arg
50					55					60					
His	Ser	Gln	Thr	Leu	Lys	Ala	Met	Val	Gln	Ala	Trp	Pro	Phe	Thr	Cys
65					70					75					80
Leu	Pro	Leu	Gly	Val	Leu	Met	Lys	Gly	Gln	His	Leu	His	Leu	Glu	Thr
				85					90					95	
Phe	Lys	Ala	Val	Leu	Asp	Gly	Leu	Asp	Val	Leu	Leu	Ala	Gln	Glu	Val
				100					105					110	
Arg	Pro	Arg	Arg	Trp	Lys	Leu	Gln	Val	Leu	Asp	Leu	Arg	Lys	Asn	Ser
				115					120					125	
His	Gln	Asp	Phe	Trp	Thr	Val	Trp	Ser	Gly	Asn	Arg	Ala	Ser	Leu	Tyr
				130					135					140	
Ser	Phe	Pro	Glu	Pro	Glu	Ala	Ala	Gln	Pro	Met	Thr	Lys	Lys	Arg	Lys
145					150					155					160
Val	Asp	Gly	Leu	Ser	Thr	Glu	Ala	Glu	Gln	Pro	Phe	Ile	Pro	Val	Glu
				165					170					175	
Val	Leu	Val	Asp	Leu	Phe	Leu	Lys	Glu	Gly	Ala	Cys	Asp	Glu	Leu	Phe
				180					185					190	
Ser	Tyr	Leu	Ile	Glu	Lys	Val	Lys	Arg	Lys	Lys	Asn	Val	Leu	Arg	Leu
				195					200					205	
Cys	Cys	Lys	Lys	Leu	Lys	Ile	Phe	Ala	Met	Pro	Met	Gln	Asp	Ile	Lys
				210					215					220	
Met	Ile	Leu	Lys	Met	Val	Gln	Leu	Asp	Ser	Ile	Glu	Asp	Leu	Glu	Val
225					230					235					240
Thr	Cys	Thr	Trp	Lys	Leu	Pro	Thr	Leu	Ala	Lys	Phe	Ser	Pro	Tyr	Leu
				245					250					255	
Gly	Gln	Met	Ile	Asn	Leu	Arg	Arg	Leu	Leu	Leu	Ser	His	Ile	His	Ala
				260					265					270	
Ser	Ser	Tyr	Ile	Ser	Pro	Glu	Lys	Glu	Glu	Gln	Tyr	Ile	Ala	Gln	Phe
				275					280					285	
Thr	Ser	Gln	Phe	Leu	Ser	Leu	Gln	Cys	Leu	Gln	Ala	Leu	Tyr	Val	Asp
				290					295					300	
Ser	Leu	Phe	Phe	Leu	Arg	Gly	Arg	Leu	Asp	Gln	Leu	Leu	Arg	His	Val
305					310					315					320
Met	Asn	Pro	Leu	Glu	Thr	Leu	Ser	Ile	Thr	Asn	Cys	Arg	Leu	Ser	Glu
				325					330					335	
Gly	Asp	Val	Met	His	Leu	Ser	Gln	Ser	Pro	Ser	Val	Ser	Gln	Leu	Ser
				340					345					350	
Val	Leu	Ser	Leu	Ser	Gly	Val	Met	Leu	Thr	Asp	Val	Ser	Pro	Glu	Pro
				355					360					365	
Leu	Gln	Ala	Leu	Leu	Glu	Arg	Ala	Ser	Ala	Thr	Leu	Gln	Asp	Leu	Val
				370					375					380	
Phe	Asp	Glu	Cys	Gly	Ile	Thr	Asp	Asp	Gln	Leu	Leu	Ala	Leu	Leu	Pro
385					390					395					400
Ser	Leu	Ser	His	Cys	Ser	Gln	Leu	Thr	Thr	Leu	Ser	Phe	Tyr	Gly	Asn
				405					410					415	
Ser	Ile	Ser	Ile	Ser	Ala	Leu	Gln	Ser	Leu	Leu	Gln	His	Leu	Ile	Gly
				420					425					430	
Leu	Ser	Asn	Leu	Thr	His	Val	Leu	Tyr	Pro	Val	Pro	Leu	Glu	Ser	Tyr
				435					440					445	
Glu	Asp	Ile	His	Gly	Thr	Leu	His	Leu	Glu	Arg	Leu	Ala	Tyr	Leu	His
				450					455					460	
Ala	Arg	Leu	Arg	Glu	Leu	Leu	Cys	Glu	Leu	Gly	Arg	Pro	Ser	Met	Val
465					470					475					480
Trp	Leu	Ser	Ala	Asn	Pro	Cys	Pro	His	Cys	Gly	Asp	Arg	Thr	Phe	Tyr
				485					490					495	
Asp	Pro	Glu	Pro	Ile	Leu	Cys	Pro	Cys	Phe	Met	Pro	Asn			
				500					505						

<210> 78
 <211> 261
 <212> PRT
 <213> Homo sapiens

<400> 78
 Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1 5 10 15
 Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
 20 25 30
 Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
 35 40 45
 Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
 50 55 60
 His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
 65 70 75 80
 Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
 85 90 95
 Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
 100 105 110
 Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
 115 120 125
 Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
 130 135 140
 Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
 145 150 155 160
 Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
 165 170 175
 His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
 180 185 190
 Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
 195 200 205
 Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
 210 215 220
 Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro
 225 230 235 240
 Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
 245 250 255
 Ile Val Ala Asn Pro
 260

<210> 79
 <211> 123
 <212> PRT
 <213> Homo sapiens

<400> 79
 Met Lys Ala Val Leu Leu Ala Leu Leu Met Ala Gly Leu Ala Leu Gln
 1 5 10 15
 Pro Gly Thr Ala Leu Leu Cys Tyr Ser Cys Lys Ala Gln Val Ser Asn
 20 25 30
 Glu Asp Cys Leu Gln Val Glu Asn Cys Thr Gln Leu Gly Glu Gln Cys
 35 40 45
 Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr Val Ile Ser Lys
 50 55 60
 Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp Tyr Tyr Val Gly
 65 70 75 80
 Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys Asn Ala Ser Gly
 85 90 95
 Ala His Ala Leu Gln Pro Ala Ala Ala Ile Leu Ala Leu Leu Pro Ala

100
Leu Gly Leu Leu Trp Gly Pro Gly Gln Leu
115 120

110

<210> 80
<211> 2817
<212> DNA
<213> Homo sapiens

<400> 80
gtgctaaaaa gatgccttct tcatttggct gtgatagggt ctttgtggct gtgggggcta 60
caaaagtacc cagaaaccag gactggcttg gtgtctcaag gcaactcaga accaaagcct 120
ggaacaggca gctgtatcca gagtggacag aagcccagag acttgactgc tggagagggt 180
gtcaagtgtc cctcaaggctc agtaatgatg ggcctacact gattggtgca aatgcctcct 240
tctctattgc cttgaacttc cctggaagcc aaaaggattt gccagatggg cagggttatct 300
gggtcaacaa taccatcatc aatgggagcc aggtgtgggg aggacagcca gtgtatcccc 360
aggaaactga cgatgcctgc atcttccttg atgggtggacc ttgccatctt ggctcttggg 420
ctcagaagag aagctttgtt tatgtctgga agacctgggg tgagggactc ctttctcagc 480
ctatcatcca cacttgtgtt tacttcttct tacctgatca ctttctttt ggccgcccct 540
tccaccttaa cttctgtgat tttctctaata ttctatttct ctcttagatc ttttctcttt 600
cttagcacct agcccccttc aagctctatc ataattcttt ctggcaactc ttggcctcaa 660
ttgtagtcct accccatgga atgcctcatt aggaccctt ccctgtcccc ccataatcaca 720
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agcctggcgc cccttcctag gtcatgcctc ctcccctagg gaatgggtccc agcacgagt 660
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ttctgtagaa aataaaactg agctacgaaa aa 752

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<210> 85

<211> 2148

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(2)

<223> n = A,T,C or G

<400> 85

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actctctgag gaaaaacat tttgattatt actctcagac gtgcgtggca acaagtgact 180
gagacctaga aatccaagcg ttggaggtcc tgaggccagc ctaagtgcgt tcaaaatgga 240
acgaaggcgt ttgtggggtt ccattcagag ccgatacatc agcatgagtg tgtggacaag 300
cccacggaga cttgtggagc tggcagggca gagcctgctg aaggatgagg ccctggccat 360

```

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tctgggagtg ctgatgaagg gacaacatct tcacctggag accttcaaag ctgtgcttga 540
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acaaatgttc agtgtgagtg aggaaaacat gttcagtgag gaaaaaacat tcagacaaat 1920
gttcagtgag gaaaaaaagg ggaagttggg gataggcaga tgttgacttg aggagttaat 1980
gtgatctttg gggagataca tcttatagag tttagaaatg aatctgaatt tctaaaggga 2040
gattctggct tgggaagtac atgtaggagt taatccctgt gtagactgtt gtaaagaaac 2100
tgttgaaaaat aaagagaagc aatgtgaagc aaaaaaaaa aaaaaaaa 2148

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<210> 86

<211> 1466

<212> DNA

<213> Homo sapiens

<400> 86

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gggaggettg gagtgcgaga agcattccca acctggcag gtgcttgttg cctctcgtgg 180
cagggcagtc tgcggcggtg ttctgtgtga ccccagtggt gtcctcacag ctgcccactg 240
catcaggaac aaaagcgtga tctgtgtggg tcggcacagc ctgtttcctc ctgaagacac 300
aggccaggta tttcaggtca gccacagctt cccacacccg ctctacgata tgagcctcct 360
gaagaatcga ttctcaggg caggtgatga ctccagccac gacctcatgc tgcctcgct 420
gtcagagcct gccagctca cggatgctgt gaaggtcatg gacctgcca cccaggagcc 480
agcactggg accacctgct acgcctcagg ctggggcagc attgaaccag aggagttct 540
gaccccaaag aaacttcagt gtgtggacct ccatgttatt tccaatgacg tgtgtgcgca 600
agttcacctc cagaaggtga ccaagttcat gctgtgtgct ggacgctgga cagggggcaa 660
aagcacctgc tcgggtgatt ctgggggccc acttgtctgt aatgggtgtg ttcaaggtat 720
cacgtcatgg ggcagtgaa catgtgccct gccgaaagg ccttccctgt acaccaaggt 780
ggtgcattac cggaagtgg tcaaggacac catcgtggcc aaccctgag caccctatc 840
aaccctctat ttagtaaac ttggaacctt ggaaatgacc aggccaagac tcaagcctcc 900
ccagttctac tgacctttgt ccttaggtgt gaggtccagg gttgctagga aaagaaatca 960
gcagacacag gtgtagacca gagtgtttct taaatggtgt aattttgtcc tctctgtgtc 1020
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gatggggtgt ctgtgttatt tgtgggttac agagatgaaa gaggggtggg atccacactg 1140
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gcacaacgca ccagacactc acagcaagga tggagctgaa aacataaccc actctgtcct 1260
ggaggcactg ggaagcctag agaaggctgt gagccaagga gggagggctc tcctttggca 1320
tgggatgggg atgaagtaag gagagggact ggacccctg gaagctgatt cactatgggg 1380
ggaggtgtat tgaagtctc cagacaaccc tcagatttga tgatttccta gtagaactca 1440

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cagaaataaa gagctgttat actgtg

1466

<210> 87
 <211> 990
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(990)
 <223> n = A,T,C or G

<400> 87
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 tgcagccagg cactgccctg ctgtgctact cctgcaaagc ccaggtgagc aacgaggact 120
 gcctgcagggt ggagaactgc acccagctgg gggagcagtg ctggaccgcg cgcacccgcg 180
 cagttggcct cctgaccgtc atcagcaaag gctgcagctt gaactgcgtg gatgactcac 240
 aggactacta cgtgggcaag aagaacatca cgtgctgtga caccgacttg tgcaacgcca 300
 gcggggccca tgccctgcag ccggctgccc ccacccctg gctgctccct gcaactcgccc 360
 tgctgctctg gggaccgggc cagctatagg ctctgggggg ccccgctgca gccacactg 420
 ggtgtggtgc cccaggcctt tgtgccactc ctcacagaac ctggcccagt gggagcctgt 480
 cctggttctt gaggcacatc ctaacgcaag tttgaccatg tatgtttgca ccccttttcc 540
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 tganacanat ccgcntgcag atggcccctc caacnnttn tggtgntgtt tccatggccc 660
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 ccacccatt tatgaattga gccaggtttg gtccgtggtg tccccgcac ccagcagggg 780
 acaggcaatc aggagggccc agtaaaggct gagatgaagt ggactgagta gaactggagg 840
 acaagagttg acgtgagttc ctgggagttt ccagagatgg ggcctggagg cctggaggaa 900
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<210> 88
 <211> 702
 <212> PRT
 <213> Homo sapiens

<400> 88
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 Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
 35 40 45
 Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
 50 55 60
 Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
 65 70 75 80
 Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser
 85 90 95
 Gly Arg Glu Ile Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Ile
 100 105 110
 Ile Gln Asn Asp Thr Gly Phe Tyr Thr Leu His Val Ile Lys Ser Asp
 115 120 125
 Leu Val Asn Glu Glu Ala Thr Gly Gln Phe Arg Val Tyr Pro Glu Leu
 130 135 140
 Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro Val Glu Asp Lys
 145 150 155 160
 Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Ala Thr Tyr
 165 170 175
 Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
 180 185 190

Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn Val Thr Arg Asn
 195 200 205
 Asp Thr Ala Ser Tyr Lys Cys Glu Thr Gln Asn Pro Val Ser Ala Arg
 210 215 220
 Arg Ser Asp Ser Val Ile Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro
 225 230 235 240
 Thr Ile Ser Pro Leu Asn Thr Ser Tyr Arg Ser Gly Glu Asn Leu Asn
 245 250 255
 Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe
 260 265 270
 Val Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn
 275 280 285
 Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys Gln Ala His Asn Ser
 290 295 300
 Asp Thr Gly Leu Asn Arg Thr Thr Val Thr Thr Ile Thr Val Tyr Ala
 305 310 315 320
 Glu Pro Pro Lys Pro Phe Ile Thr Ser Asn Asn Ser Asn Pro Val Glu
 325 330 335
 Asp Glu Asp Ala Val Ala Leu Thr Cys Glu Pro Glu Ile Gln Asn Thr
 340 345 350
 Thr Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg
 355 360 365
 Leu Gln Leu Ser Asn Asp Asn Arg Thr Leu Thr Leu Leu Ser Val Thr
 370 375 380
 Arg Asn Asp Val Gly Pro Tyr Glu Cys Gly Ile Gln Asn Glu Leu Ser
 385 390 395 400
 Val Asp His Ser Asp Pro Val Ile Leu Asn Val Leu Tyr Gly Pro Asp
 405 410 415
 Asp Pro Thr Ile Ser Pro Ser Tyr Thr Tyr Tyr Arg Pro Gly Val Asn
 420 425 430
 Leu Ser Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser
 435 440 445
 Trp Leu Ile Asp Gly Asn Ile Gln Gln His Thr Gln Glu Leu Phe Ile
 450 455 460
 Ser Asn Ile Thr Glu Lys Asn Ser Gly Leu Tyr Thr Cys Gln Ala Asn
 465 470 475 480
 Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val Lys Thr Ile Thr Val
 485 490 495
 Ser Ala Glu Leu Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro
 500 505 510
 Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Ala Gln
 515 520 525
 Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser
 530 535 540
 Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn
 545 550 555 560
 Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys Gly Ile Gln Asn Ser
 565 570 575
 Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu Asp Val Leu Tyr Gly
 580 585 590
 Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser Ser Tyr Leu Ser Gly
 595 600 605
 Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser Asn Pro Ser Pro Gln
 610 615 620
 Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln His Thr Gln Val Leu
 625 630 635 640
 Phe Ile Ala Lys Ile Thr Pro Asn Asn Asn Gly Thr Tyr Ala Cys Phe
 645 650 655
 Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser Ile Val Lys Ser Ile
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 Thr Val Ser Ala Ser Gly Thr Ser Pro Gly Leu Ser Ala Gly Ala Thr

675 680 685
 Val Gly Ile Met Ile Gly Val Leu Val Gly Val Ala Leu Ile
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<210> 89
 <211> 2974
 <212> DNA
 <213> Homo sapiens

<400> 89
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 gtaataggaa ctcaacaagc taccacaggg cccgcataca gtggtcgaga gataatatac 420
 cccaatgcat ccctgctgat ccagaacatc atccagaatg acacaggatt ctacacccta 480
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<210> 90
 <211> 1255
 <212> PRT
 <213> Homo sapiens

<400> 90
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 1 5 10 15
 Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30
 Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45
 Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60
 Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80
 Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95
 Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110
 Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125
 Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
 130 135 140
 Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160
 Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175
 Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190
 His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205
 Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220
 Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240
 Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255
 His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270
 Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285
 Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300
 Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320
 Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335
 Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
 340 345 350
 Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
 355 360 365
 Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
 370 375 380
 Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
 385 390 395 400
 Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
 405 410 415
 Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
 420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
 435 440 445
 Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
 450 455 460
 Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
 465 470 475 480
 Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
 485 490 495
 Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
 500 505 510
 Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
 515 520 525
 Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
 530 535 540
 Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
 545 550 555 560
 Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
 565 570 575
 Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
 580 585 590
 Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
 595 600 605
 Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
 610 615 620
 Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
 625 630 635 640
 Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Val Ser
 645 650 655
 Ala Val Val Gly Ile Leu Leu Val Val Leu Gly Val Val Phe Gly
 660 665 670
 Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg
 675 680 685
 Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly
 690 695 700
 Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu
 705 710 715 720
 Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys
 725 730 735
 Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile
 740 745 750
 Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu
 755 760 765
 Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg
 770 775 780
 Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu
 785 790 795 800
 Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg
 805 810 815
 Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly
 820 825 830
 Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala
 835 840 845
 Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
 850 855 860
 Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp
 865 870 875 880
 Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg
 885 890 895
 Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val
 900 905 910
 Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala

915	920	925
Arg Glu Ile Pro Asp Leu	Leu Glu Lys Gly Glu Arg	Leu Pro Gln Pro
930	935	940
Pro Ile Cys Thr Ile Asp	Val Tyr Met Ile Met	Val Lys Cys Trp Met
945	950	955
Ile Asp Ser Glu Cys Arg	Pro Arg Phe Arg	Glu Leu Val Ser Glu Phe
965	970	975
Ser Arg Met Ala Arg	Asp Pro Gln Arg	Phe Val Val Ile Gln Asn Glu
980	985	990
Asp Leu Gly Pro Ala Ser	Pro Leu Asp Ser Thr	Phe Tyr Arg Ser Leu
995	1000	1005
Leu Glu Asp Asp Asp	Met Gly Asp Leu Val	Asp Ala Glu Glu Tyr Leu
1010	1015	1020
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<210> 91

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<212> DNA

<213> Homo sapiens

<400> 91

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<210> 92

<211> 976

<212> PRT

<213> Homo sapiens

<400> 92

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Gly Asn Ser Asp Cys His Tyr Gln Glu Gly Leu Lys Asp Ser Asp Leu
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His Gly Glu Leu Arg Val Gln Ala Glu Asn Ser Arg Leu Glu Met His
          225          230          235          240
Phe Lys Leu Lys Glu Asp Tyr Glu Lys Ile Gln His Leu Glu Gln Glu
          245          250          255
Tyr Lys Lys Glu Ile Asn Asp Lys Glu Lys Gln Val Ser Leu Leu Leu
          260          265          270
Ile Gln Ile Thr Glu Lys Glu Asn Lys Met Lys Asp Leu Thr Phe Leu
          275          280          285
Leu Glu Glu Ser Arg Asp Lys Val Asn Gln Leu Glu Glu Lys Thr Lys
          290          295          300
Leu Gln Ser Glu Asn Leu Lys Gln Ser Ile Glu Lys Gln His His Leu
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Thr Lys Glu Leu Glu Asp Ile Lys Val Ser Leu Gln Arg Ser Val Ser
          325          330          335
Thr Gln Lys Ala Leu Glu Glu Asp Leu Gln Ile Ala Thr Lys Thr Ile
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Cys Gln Leu Thr Glu Glu Lys Glu Thr Gln Met Glu Glu Ser Asn Lys
          355          360          365
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			500					505					510	Lys
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		515					520					525		Lys
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Gln	Ile	Glu	Asn	Leu	Gln	Glu	Thr	Glu	Thr	Gln	Leu	Arg	Asn	Glu
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			580					585				590		Cys
Lys	Leu	Asp	Lys	Ser	Glu	Glu	Asn	Cys	Asn	Asn	Leu	Arg	Lys	Gln
		595				600					605			Val
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			645					650						655
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Lys	Asp	Lys	Arg	Asp	Tyr	Leu	Trp	Thr	Ser	Ala	Lys	Asn	Thr	Leu
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<210> 93

<211> 3393

<212> DNA

<213> Homo sapiens

<400> 93

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<210> 94

<211> 188

<212> PRT

<213> Homo sapiens

<400> 94

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      35          40          45
Val Tyr Met Lys Leu Asn Tyr Glu Val Met Thr Lys Leu Gly Phe Lys
      50          55          60
Val Thr Leu Pro Pro Phe Met Arg Ser Lys Arg Ala Ala Asp Phe His
      65          70          75          80
Gly Asn Asp Phe Gly Asn Asp Arg Asn His Arg Asn Gln Val Glu Arg
      85          90          95
Pro Gln Met Thr Phe Gly Ser Leu Gln Arg Ile Phe Pro Lys Ile Met
      100          105          110
Pro Lys Lys Pro Ala Glu Glu Glu Asn Gly Leu Lys Glu Val Pro Glu
      115          120          125
Ala Ser Gly Pro Gln Asn Asp Gly Lys Gln Leu Cys Pro Pro Gly Asn
      130          135          140
Pro Ser Thr Leu Glu Lys Ile Asn Lys Thr Ser Gly Pro Lys Arg Gly
      145          150          155          160
Lys His Ala Trp Thr His Arg Leu Arg Glu Arg Lys Gln Leu Val Val
      165          170          175
Tyr Glu Glu Ile Ser Asp Pro Glu Glu Asp Asp Glu
      180          185

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<210> 95

<211> 576

<212> DNA

<213> Homo sapiens

<400> 95

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aaatcctcgg agaaaatcgt ctatgtgtat atgaagctaa actatgaggt catgactaaa 180
ctaggtttca aggtcaccct ccacctttc atgcgtagta aacgggctgc agacttcac 240
gggaatgatt ttggtaacga tcgaaaccac aggaatcagg ttgaacgtcc tcagatgact 300
ttcggcagcc tccagagaat cttcccgaag atcatgccca agaagccagc agaggaagaa 360

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aatggtttga aggaagtgcc agaggcatct ggcccacaaa atgatgggaa acagctgtgc 420
 cccccgggaa atccaagtac cttggagaag attaacaaga catctggacc caaaaggggg 480
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<210> 96

<211> 94

<212> PRT

<213> Homo sapiens

<400> 96

Pro Ala Thr Gln Arg Gln Asp Pro Ala Ala Ala Gln Glu Gly Glu Asp
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 20 25 30
 Glu Gln Gly His Pro Gln Thr Gly Cys Glu Cys Glu Asp Gly Pro Asp
 35 40 45
 Gly Gln Glu Met Asp Pro Pro Asn Pro Glu Glu Val Lys Thr Pro Glu
 50 55 60
 Glu Glu Met Arg Ser His Tyr Val Ala Gln Thr Gly Ile Leu Trp Leu
 65 70 75 80
 Leu Met Asn Asn Cys Phe Leu Asn Leu Ser Pro Arg Lys Pro
 85 90

<210> 97

<211> 646

<212> DNA

<213> Homo sapiens

<400> 97

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 cctatgcggc ccgagcagtt cagtgatgaa gtggaaccag caacacctga agaaggggaa 180
 ccagcaactc aacgtcagga tcctgcagct gctcaggagg gagaggatga gggagcatct 240
 gcagggtcaag ggccgaagcc tgaagctgat agccaggaac agggtcaccc acagactggg 300
 tgtgagtgtg aagatggtcc tgatgggcag gagatggacc cgccaaatcc agaggaggtg 360
 aaaacgcctg aagaagagat gaggtctcac tatgttgccc agactgggat tctctggctt 420
 ttaatgaaca attgcttctt aaatctttcc ccacggaaac cttgagtgaac tgaatatca 480
 aatggcgaga gaccgttttag ttctatcat ctgtggcatg tgaagggcaa tcacagtgtt 540
 aaaagaagac atgctgaaat gttgcaggct gctcctatgt tggaaaattc ttcattgaag 600
 ttctcccaat aaagctttac agccttctgc aaagaaaaaa aaaaaa 646

<210> 98

<211> 98

<212> PRT

<213> Homo sapiens

<400> 98

His Cys Pro Thr Glu Asn Glu Pro Asp Leu Ala Gln Cys Phe Phe Cys
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 20 25 30
 His Lys Lys His Ser Ser Gly Cys Ala Phe Leu Ser Val Lys Lys Gln
 35 40 45
 Phe Glu Glu Leu Thr Leu Gly Glu Phe Leu Lys Leu Asp Arg Glu Arg
 50 55 60
 Ala Lys Asn Lys Ile Ala Lys Glu Thr Asn Asn Lys Lys Lys Glu Phe
 65 70 75 80
 Glu Glu Thr Ala Lys Lys Val Arg Arg Ala Ile Glu Gln Leu Ala Ala
 85 90 95

Met Asp

<210> 99
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 ctggcccttc ttggagggtc ggcctgcac cccggagcgg atggccgagg ctggcttcat 180
 ccactgcccc actgagaacg agccagactt ggcccagtggt ttcttctgct tcaaggagct 240
 ggaaggctgg gagccagatg acgaccccat agaggaacat aaaaagcatt cgtccggttg 300
 cgctttcctt tctgtcaaga agcagtttga agaattaacc cttggtgaat ttttgaact 360
 ggacagagaa agagccaaga acaaaattgc aaaggaaacc aacaataaga agaaagaatt 420
 tgaggaaact gcgaagaaag tgcgcgtgct catcgagcag ctggctgcca tggattgagg 480
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 gtgccaccag ccttcctgtg ggccccttag caatgtctta ggaaaggaga tcaacatttt 600
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 ggtgcctgtt gaatctgagc tgcaggttcc ttatctgtca cacctgtgcc tcctcagagg 960
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 tattttgttt gaattgttaa ttacagaaat agcacaaact acaattaaaa ctaagcaca 1140
 agccattcta agtcattggg gaaacggggt gaacttcagg tggatgagga gacagaatag 1200
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 <211> 74
 <212> PRT
 <213> Homo sapiens

<400> 100
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 Ser Leu His Val Gly Thr Gln Cys Ala Leu Thr Arg Arg Cys Pro Gln
 20 25 30
 Glu Gly Phe Asp His Arg Asp Ser Lys Val Ser Leu Gln Glu Lys Asn
 35 40 45
 Cys Glu Pro Val Val Pro Asn Ala Pro Pro Ala Tyr Glu Lys Leu Ser
 50 55 60
 Ala Glu Gln Ser Pro Pro Tyr Ser Pro
 65 70

<210> 101
 <211> 1524
 <212> DNA
 <213> Homo sapiens

<400> 101

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gagaagatgc tcaattcatc tatggttacc ccaagaaggg gcacggccac tcttacacca 120
cggtggaaga ggccgctggg atcgcatcc tgacagtgat cctgggagtc ttactgctca 180
tcggctgttg gtattgtaga agacgaaatg gatacagagc cttgatggat aaaagtcttc 240
atgttggcac tcaatgtgcc ttaacaagaa gatgcccaca agaagggttt gatcatcggt 300
acagcaaaagt gtctcttcaa gagaaaaact gtgaacctgt ggttcccaat gctccacctg 360
cttatgagaa actctctgca gaacagtcac caccacctta ttcaccttaa gagccagcga 420
gacacctgag acatgctgaa attatttctc tcacactttt gottgaattt aatacagaca 480
tctaattgttc tcttttgaa tggtgtagga aaaatgcaag ccactctctaa taataagtca 540
gtgttaaaat tttagtaggt ccgctagcag tactaatcat gtgaggaaat gatgagaaat 600
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gtaatgttag taaatccatg gtgttatttt ctgagagaca gaattcaagt ggggtattctg 720
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acccttgacc acatgaactg tacacagaat tgttccagta ctatggagtg ctcacaaagg 840
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aatcataaag gatcagagat tctg 1524

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<210> 102

<211> 43

<212> PRT

<213> Homo sapiens

<400> 102

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Met Ala Ala Arg Ala Val Phe Leu Ala Leu Ser Ala Gln Leu Leu Gln
 1           5           10           15
Ala Arg Leu Met Lys Glu Glu Ser Pro Val Val Ser Trp Arg Leu Glu
      20           25           30
Pro Glu Asp Gly Thr Ala Leu Cys Phe Ile Phe
      35           40

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<210> 103

<211> 1004

<212> DNA

<213> Homo sapiens

<400> 103

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gtggtggcaa cagagatggc agcgcagctg gagtgttagg agggcggcct gagcggtagg 180
agtggggctg gagcagtaag atggcggcca gagcggtttt tctggcattg tctgccagc 240
tgctccaagc caggctgatg aaggaggagt cccctgtggt gagctggagg ttggagcctg 300
aagacggcac agctctgtgc ttcactttct gaggttgggg cagccacggg gatggagacg 360
gcagctcaac aggagcaata ggaggagatg gagtttcaact gtgtcagcca ggtgggtctc 420
gatctctga cctcgtgatc cgccgcctt ggccttccaa agtgccgaga ttacagcgat 480
gtgcattttg taagcacttt ggagccacta tcaaagtctg tgaagagaaa tgtaccaga 540
tgtatcatta tccttgtgct gcaggagccg gctccttcca ggatttcagt cacatcttcc 600
tgctttgtcc agaacacatt gaccaagctc ctgaaagatg taagtttact acgcatagac 660
ttttaaactt caaccaatgt atttactgaa aataacaaat gttgtaaatt cctgagtg 720
tattctactt gtattaaaag gtaataatac ataatacatta aaatctgagg gatcattg 780

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agagattggtt ggggagggaa atgttatcaa cggtttcatt gaaattaaat ccaaaaagtt 840
 atttcctcag aaaaatcaaa taaagtttgc atgtttttta ttcttaaaac attttaaaaa 900
 ccactgtaga atgatgtaaa tagggactgt gcagtatttc tgacatatat tataaaatta 960
 ttaaaaagtc aatcagtatt caacatcttt tacactaaaa agcc 1004

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 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 104
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<210> 105
 <211> 263
 <212> PRT
 <213> Homo sapiens

<400> 105
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 20 25 30
 Glu Gln His Ser Gln Pro Trp Gln Ala Ala Leu Tyr His Phe Ser Thr
 35 40 45
 Phe Gln Cys Gly Gly Ile Leu Val His Arg Gln Trp Val Leu Thr Ala
 50 55 60
 Ala His Cys Ile Ser Asp Asn Tyr Gln Leu Trp Leu Gly Arg His Asn
 65 70 75 80
 Leu Phe Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser
 85 90 95
 Phe Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn His Thr Arg
 100 105 110
 Gln Ala Asp Glu Asp Tyr Ser His Asp Leu Met Leu Leu Arg Leu Thr
 115 120 125
 Glu Pro Ala Asp Thr Ile Thr Asp Ala Val Lys Val Val Glu Leu Pro
 130 135 140
 Thr Gln Glu Pro Glu Val Gly Ser Thr Cys Leu Ala Ser Gly Trp Gly
 145 150 155 160
 Ser Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp Leu Gln Cys Val
 165 170 175
 Asp Leu Lys Ile Leu Pro Asn Asp Glu Cys Glu Lys Ala His Val Gln
 180 185 190
 Lys Val Thr Asp Phe Met Leu Cys Val Gly His Leu Glu Gly Gly Lys
 195 200 205
 Asp Thr Cys Val Gly Asp Ser Gly Gly Pro Leu Met Cys Asp Gly Val
 210 215 220
 Leu Gln Gly Val Thr Ser Trp Gly Tyr Val Pro Cys Gly Thr Pro Asn
 225 230 235 240
 Lys Pro Ser Val Ala Val Arg Val Leu Ser Tyr Val Lys Trp Ile Glu
 245 250 255
 Asp Thr Ile Ala Glu Asn Ser
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<210> 106
 <211> 270
 <212> PRT
 <213> Homo sapiens

<400> 106

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Pro Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu
 1           5           10           15
Ser Cys Gly Asp Pro Thr Tyr Pro Pro Tyr Val Thr Arg Val Val Gly
          20           25           30
Gly Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln
          35           40           45
Tyr Ser Ser Asn Gly Lys Trp Tyr His Thr Cys Gly Gly Ser Leu Ile
 50           55           60
Ala Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg
65           70           75           80
Thr Tyr Arg Val Gly Leu Gly Arg His Asn Leu Tyr Val Ala Glu Ser
          85           90           95
Gly Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp
          100          105          110
Asn Ser Asn Gln Ile Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu
          115          120          125
Ala Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro
130          135          140
Pro Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly
145          150          155          160
Trp Gly Arg Leu Gln Thr Asn Gly Ala Val Pro Asp Val Leu Gln Gln
          165          170          175
Gly Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Ala Trp
          180          185          190
Trp Gly Ser Ser Val Lys Thr Ser Met Ile Cys Ala Gly Gly Asp Gly
195          200          205
Val Ile Ser Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln
210          215          220
Ala Ser Asp Gly Arg Trp Gln Val His Gly Ile Val Ser Phe Gly Ser
225          230          235          240
Arg Leu Gly Cys Asn Tyr Tyr His Lys Pro Ser Val Phe Thr Arg Val
          245          250          255
Ser Asn Tyr Ile Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
          260          265          270

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<210> 107

<211> 270

<212> PRT

<213> Homo sapiens

<400> 107

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Pro Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu
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Ser Cys Gly Val Ser Thr Tyr Ala Pro Asp Met Ser Arg Met Leu Gly
          20           25           30
Gly Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln
          35           40           45
Tyr Ser Ser Asn Gly Gln Trp Tyr His Thr Cys Gly Gly Ser Leu Ile
 50           55           60
Ala Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg
65           70           75           80
Ile Tyr Arg Val Met Leu Gly Gln His Asn Leu Tyr Val Ala Glu Ser
          85           90           95
Gly Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp
          100          105          110
Asn Ser Asn Gln Val Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu
          115          120          125
Ala Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro

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130		135		140											
Pro	Ala	Gly	Thr	Ile	Leu	Pro	Asn	Asn	Tyr	Pro	Cys	Tyr	Val	Thr	Gly
145					150					155					160
Trp	Gly	Arg	Leu	Gln	Thr	Asn	Gly	Ala	Leu	Pro	Asp	Asp	Leu	Lys	Gln
			165							170					175
Gly	Arg	Leu	Leu	Val	Val	Asp	Tyr	Ala	Thr	Cys	Ser	Ser	Ser	Gly	Trp
			180					185					190		
Trp	Gly	Ser	Thr	Val	Lys	Thr	Asn	Met	Ile	Cys	Ala	Gly	Gly	Asp	Gly
		195				200						205			
Val	Ile	Cys	Thr	Cys	Asn	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Asn	Cys	Gln
	210					215					220				
Ala	Ser	Asp	Gly	Arg	Trp	Glu	Val	His	Gly	Ile	Gly	Ser	Leu	Thr	Ser
225					230					235					240
Val	Leu	Gly	Cys	Asn	Tyr	Tyr	Tyr	Lys	Pro	Ser	Ile	Phe	Thr	Arg	Val
			245						250					255	
Ser	Asn	Tyr	Asn	Asp	Trp	Ile	Asn	Ser	Val	Ile	Ala	Asn	Asn		
			260					265					270		

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 <213> Homo sapiens

<400> 108
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<210> 109
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<400> 109
 Tyr Asp Leu Phe Val Trp Met His Tyr Tyr
 1 5 10

<210> 110
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<400> 110
 Asp Leu Phe Val Trp Met His Tyr Tyr
 1 5

<210> 111
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<400> 111
 Asp Ala Leu Leu Gly Gly Ser Glu Ile
 1 5

<210> 112
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<212> PRT
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<400> 112
Gly Ser Glu Ile Trp Arg Asp Ile Asp Phe
1 5 10

<210> 113
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<212> PRT
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<400> 113
Ser Glu Ile Trp Arg Asp Ile Asp Phe
1 5

<210> 114
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<400> 114
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1 5

<210> 115
<211> 10
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<400> 115
Leu Gln Glu Val Tyr Pro Glu Ala Asn Ala
1 5 10

<210> 116
<211> 10
<212> PRT
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<400> 116
Glu Val Tyr Pro Glu Ala Asn Ala Pro Ile
1 5 10

<210> 117
<211> 9
<212> PRT
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<400> 117
Val Tyr Pro Glu Ala Asn Ala Pro Ile
1 5

<210> 118
<211> 8
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<213> Homosapiens

<400> 118

Tyr Pro Glu Ala Asn Ala Pro Ile
1 5

<210> 119

<211> 10

<212> PRT

<213> Homosapiens

<400> 119

Tyr Pro Glu Ala Asn Ala Pro Ile Gly His
1 5 10

<210> 120

<211> 10

<212> PRT

<213> Homosapiens

<400> 120

Ala Pro Ile Gly His Asn Arg Glu Ser Tyr
1 5 10

<210> 121

<211> 9

<212> PRT

<213> Homosapiens

<400> 121

Pro Ile Gly His Asn Arg Glu Ser Tyr
1 5

<210> 122

<211> 10

<212> PRT

<213> Homosapiens

<400> 122

Pro Ile Gly His Asn Arg Glu Ser Tyr Met
1 5 10

<210> 123

<211> 10

<212> PRT

<213> Homosapiens

<400> 123

Ala Pro Ile Gly His Asn Arg Glu Ser Tyr
1 5 10

<210> 124

<211> 9

<212> PRT

<213> Homosapiens

<400> 124

Pro Ile Gly His Asn Arg Glu Ser Tyr
1 5

<210> 125

<211> 8

<212> PRT

<213> Homosapiens

<400> 125

Glu Ser Tyr Met Val Pro Phe Ile
1 5

<210> 126

<211> 10

<212> PRT

<213> Homosapiens

<400> 126

Glu Ser Tyr Met Val Pro Phe Ile Pro Leu
1 5 10

<210> 127

<211> 9

<212> PRT

<213> Homosapiens

<400> 127

Ser Tyr Met Val Pro Phe Ile Pro Leu
1 5

<210> 128

<211> 10

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<213> Homosapiens

<400> 128

Ser Tyr Met Val Pro Phe Ile Pro Leu Tyr
1 5 10

<210> 129

<211> 9

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Tyr Met Val Pro Phe Ile Pro Leu Tyr
1 5

<210> 130

<211> 9

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<400> 130
Met Val Pro Phe Ile Pro Leu Tyr Arg
1 5

<210> 131
<211> 10
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<400> 131
Met Val Pro Phe Ile Pro Leu Tyr Arg Asn
1 5 10

<210> 132
<211> 8
<212> PRT
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<400> 132
Val Pro Phe Ile Pro Leu Tyr Arg
1 5

<210> 133
<211> 8
<212> PRT
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<400> 133
Ile Pro Leu Tyr Arg Asn Gly Asp
1 5

<210> 134
<211> 10
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<400> 134
Ile Pro Leu Tyr Arg Asn Gly Asp Phe Phe
1 5 10

<210> 135
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<212> PRT
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<400> 135
Pro Leu Tyr Arg Asn Gly Asp Phe Phe
1 5

<210> 136
<211> 10
<212> PRT
<213> Homosapiens

<400> 136

Pro Leu Tyr Arg Asn Gly Asp Phe Phe Ile
1 5 10

<210> 137
<211> 10
<212> PRT
<213> Homosapiens

<400> 137
Arg Asn Gly Asp Phe Phe Ile Ser Ser Lys
1 5 10

<210> 138
<211> 9
<212> PRT
<213> Homosapiens

<400> 138
Asn Gly Asp Phe Phe Ile Ser Ser Lys
1 5

<210> 139
<211> 9
<212> PRT
<213> Homosapiens

<400> 139
Tyr Ile Lys Ser Tyr Leu Glu Gln Ala
1 5

<210> 140
<211> 9
<212> PRT
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<400> 140
Ser Tyr Leu Glu Gln Ala Ser Arg Ile
1 5

<210> 141
<211> 10
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<400> 141
Glu Gln Ala Ser Arg Ile Trp Ser Trp Leu
1 5 10

<210> 142
<211> 9
<212> PRT
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<400> 142
Gln Ala Ser Arg Ile Trp Ser Trp Leu

1 5

<210> 143
<211> 8
<212> PRT
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<400> 143
Ala Ser Arg Ile Trp Ser Trp Leu
1 5

<210> 144
<211> 9
<212> PRT
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<400> 144
Ala Ser Arg Ile Trp Ser Trp Leu Leu
1 5

<210> 145
<211> 9
<212> PRT
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<400> 145
Arg Ile Trp Ser Trp Leu Leu Gly Ala
1 5

<210> 146
<211> 9
<212> PRT
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<400> 146
Gly Pro Ala Tyr Ser Gly Arg Glu Ile
1 5

<210> 147
<211> 10
<212> PRT
<213> Homosapiens

<400> 147
Gly Pro Ala Tyr Ser Gly Arg Glu Ile Ile
1 5 10

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<211> 10
<212> PRT
<213> Homosapiens

<400> 610
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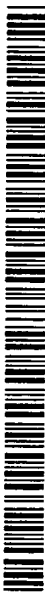


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- (71) Applicant: **MANNKIND CORPORATION** [US/US];
28903 North Avenue Paine, Valencia, CA 91355 (US).
- (72) Inventors: **SIMARD, John, J.L.**; Suite #7, 1684 Alberni Street, Vancouver, British Columbia Z6G1A6 (CA). **DIA-MOND, David, C.**; 23135 Schoenborn Street, West Hills, CA 91304 (US). **LIU, Liping**; 22228 Victory Boulevard, H-111, Woodland Hills, CA 91367 (US). **LIU, Zheng**; 22216 Victory Boulevard, C302, Woodland Hills, CA 91367 (US).
- (74) Agent: **MALLON, Joseph, J.**; **KNOBBE, MARTENS, OLSON & BEAR, LLP**, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US).
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(54) Title: EPITOPE SEQUENCES

(57) Abstract: Disclosed herein are polypeptides, including epitopes, clusters, and antigens. Also disclosed are compositions that include said polypeptides and methods for their use.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/27706

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/395, 39/00, 38/03, 48/00; A01N 63/00; C12N 15/12, 15/63

US CL : 424/184.1, 185, 1, 93.71; 435/320.1; 514/2, 44; 530/300; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/184.1, 185, 1, 93.71; 435/320.1; 514/2, 44; 530/300; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,037,135 A (KUBO et al.) 14 March 2000 (14.03.2000), see entire document.	1-82
Y	WO 94/020127 A1 (CYTEL CORPOARTION) 15 September 1994 (15.09.1994), see entire document.	1-82

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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*P	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 March 2004 (18.03.2004)

Date of mailing of the international search report

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Facsimile No. (703) 305-3230

Authorized officer

Ron Schwadron, Ph.D.

Telephone No. 571-272-1600

Y.D.R. for

INTERNATIONAL SEARCH REPORT

PCT/US03/27706

Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.1, MEDICINE/BIOTECH (compendium databases on DIALOG) search terms: inventor names, mage?, cea?, gage?, hla?,
peptid?, mhc

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